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Original Communications

LOW RESERVE KIDNEY*

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OUR knowledge of renal physiology has increased considerably during the past ten years, due greatly to the efforts of Richards, Marshall, Rehberg, and others. It seems well established today that filtration is the sole function of the kidney glomerulus and that reabsorption is the predominant function of the tubule, but that tubular secretion does occur and, furthermore, that under certain conditions such secretion may play a very important rôle in renal function.

KIDNEY FUNCTION

In order that glomerular filtration may occur, it is essential that the blood pressure in the capillaries of the glomerulus be greater than the osmotic pressure of the proteins in the blood plus the intracapsular pressure of the glomerulus. This pressure, necessary for glomerular function, has been called the "effective filtration pressure." It is, of course, clear that such filtration is further dependent upon the rate of blood flow through the kidney, in other words the rate at which new blood is brought in contact with the endothelium of the glomeruli. The other two factors that influence filtration are the area of the surface for filtration, that is, the number and size of capillary channels in the glomeruli, and the actual permeability of the glomerular membrane.

*Read before the New Orleans Graduate Medical Assembly, New Orleans, La., March, 1937.

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Concerning the reabsorption in the tubules, we know, as a result of the work of Richards and others, that this process may be selective as well as active (dependent on cell activity), but that it is not, as Ludwig stated, one of simple diffusion. Finally, Marshall and his coworkers are responsible for our knowledge of tubular secretion, a process by which materials are transported from the blood to the lumen of the tubule through gland cells.

It may be well to state that although there are still two main theories of kidney function, both of them use all three processes, filtration, reabsorption and secretion, but as Rehberg[1] states, one (secretion theory) holds that nearly all the energy is used in transporting substances from the blood, while the other (filtration-reabsorption theory) believes that the energy is mainly utilized for reabsorption into the blood.

There are many factors concerned in the maintenance and regulation of glomerular filtration and tubular reabsorption, and secretion, but it is not the purpose of this paper to deal with these in detail. Suffice it to state that glomerular blood pressure is dependent not only on the general pressure but also on vasoconstriction and vasodilator stimulation to the kidney, as well as viscosity of the blood. Diuretics such as urea, glucose and sodium chloride act, we know, because of their dilating effect on the renal vessels. That these diuretics actually may increase glomerular permeability is a possibility, not yet proved. Of very great importance, and perhaps particularly so in some types of the toxemias of pregnancy, is the fact, shown by Richards and his assistants, that at any given moment there may be different physiologic states of the glomerular circulation. They observed that the number of glomeruli with blood flowing through them may be variable, and that with vasoconstriction this number may be markedly decreased, and with vasodilatation increased. Furthermore, even in any given glomerulus or single capillary loop, the blood flow may be of irregular velocity to the extent often of intermittent flow. Sympathetic nerve stimulation, adrenalin and pituitrin are among the agents producing vasoconstriction, while glucose, caffeine, NaCl and $NaHCO_3$ act as vasodilators.

We may then describe kidney function in the human being, using a modified theory as constructed by Rehberg and based on the essentials of the two above described theories, as follows:

1. Glomerular filtration (ultrafiltration) of large quantities of protein-free fluid, amounting to about 150 c.c. per minute.
2. Active reabsorption of water from the lumen of the tubule.
3. Similarly, active reabsorption of sugar and chlorides (threshold substances).
4. Passive back diffusion of all other substances in degrees varying with the permeability of the tubular wall for each of these substances, with creatinine, to which the tubule is nonpermeable, at the one end of the scale, and alcohol, passing through most readily, at the other.
5. Tubular secretion of substances not preformed in the blood, such as ammonia.

PATHOLOGIC CONDITIONS

With this rather brief description of the present-day views of renal function, we may now turn to a consideration of a few of the factors involved in pathologic conditions affecting the kidneys.

It is quite evident that glomerular filtration will decrease if any one or more of the factors essential to filtration are affected. If the glomerular membrane be thickened, if the filtering surface be reduced in area by the partial or complete destruction of glomeruli, if the filtration pressure be reduced or if the rate of blood flow through the kidneys be decreased, glomerular filtration will be impaired. Similarly, increased or decreased permeability of the tubular wall will bring about changes in the rate and amount of water, chlorides and sugar reabsorbed, in the amount of back diffusion of urea and other substances, as well as in the ability of the tubules to secrete substances such as ammonia and hippuric acid.

It is equally evident that in the nephropathies, acute glomerulonephritis, chronic glomerulonephritis, arteriosclerotic chronic nephritis and nephrosis, some of these factors are to a lesser or greater extent involved and so kidney function affected. The filtration rate, as shown by the urea filtration rate, may be decreased in acute nephritis, is markedly decreased in the terminal stages of chronic nephritis, whether of glomerulonephritic or arteriosclerotic origin, and may likewise be low in nephrosis. Rehberg found that also in essential hypertension there may be slight reduction in the filtration rate, even before albuminuria developed.

CHRONIC NEPHRITIS

Chronic nephritis may follow an acute glomerulonephritis or it may result from a general arteriosclerosis. It is well to point out that a sclerosis involving the renal arteries but not extending to the small arteries and the afferent glomerular arterioles, is usually not accompanied by kidney disease, but as soon as these arterioles become affected by the sclerosis, a persistent hypertension is present, with later involvement of heart, brain, and kidneys, and death may be due to renal insufficiency or apoplexy or coronary disease. The arteriolosclerosis is followed by a thickening of the capsular basement membrane ultimately resulting in a complete blockage or closure of the glomerulus and a disuse atrophy of the corresponding tubule. Primary or essential hypertension, undoubtedly starts as a generalized spasm of the arterioles, and it has been suggested that this hypertension, brought about by spasm, may later produce degeneration of the arterioles and so eventuate into a malignant or progressive renal disease. This type of hypertension is the so-called "red hypertension," in contrast to the "pale hypertension" (nephritic), where, according to Volhard,[2] the peripheral and retinal arteries are narrowed, albuminuric retinitis often present, and the con-

dition perhaps dependent on a pressor substance in the blood. Volhard further believes that the "red hypertension" is not dependent on such pressure substances, but rather on a passive mechanism, based perhaps on early senescence of the arteries, a diminution of their muscular layer, overstretching of the elastic layer followed by an increased tonus of the arterioles.

The chronic nephritis complicating a pregnancy may, of course, be any of the above-stated forms, a chronic glomerulonephritis, or an arteriosclerotic chronic nephritis dependent upon arteriolar involvement, or one following essential hypertension (genuine or permanent) which has developed from a benign nephrangiosclerosis into actual and progressive kidney disease (malignant hypertension). Although it may not be absolutely essential for us to be able to differentiate between these various types, as they are present in a pregnant woman, it is most important to know that a chronic nephritis, however mild, is present, as this diseased condition is adversely affected by the pregnancy and good treatment demands termination of the pregnancy. We shall not discuss the details of diagnosis and treatment of chronic nephritis complicating pregnancy, as this has been done in earlier publications.[3, 4]

LOW RESERVE KIDNEY

Renal reserve may be of two types, native and acquired, the latter usually following kidney operation, such as unilateral nephrectomy. Reference has already been made to the work of Richards and his coworkers on the variability of the extent of glomerular filtration surfaces and on the irregular velocity of blood flow through normal glomeruli. There appears to be great variability in the number of visibly functioning glomeruli, as observed under the microscope by these and other investigators. In 1924 Schmidt and Richards[5] noted markedly different appearances in different glomeruli of the same kidney, one glomerular tuft perhaps showing many capillary channels through all of which blood is passing swiftly, while another may reveal only one capillary loop with blood passing through it. Furthermore, this picture may be constantly changing, due perhaps to vasoconstrictor or vasodilator stimuli. With such a variability of functioning glomeruli at any given time, and therefore a variability of the number of nonfunctioning or only partially functioning glomeruli, in the normal, it must be apparent that there is a large native reserve in the kidney, seldom called into play while the demands for excretion are at a normal base level. May not normal individuals differ in the extent of such native renal reserve, and may not even the same individual differ at different times in the amount of such reserve? It is a common observation that normal individuals with apparently normal kidneys may react very differently to every day stimuli, such as diuretics in the form of caffeine or water consumption. Diuresis

from drinking water is undoubtedly due to decreased tubular reabsorption. May not normal individuals also vary in their reaction to antidiuretics, e.g., pituitrin?

In 1926, Stander and Peckham[6] introduced the term "low reserve kidney" and defined it as follows:

1. An elevated blood pressure which at the end of the puerperium has dropped to a normal level. In most instances this elevation is not very marked, being approximately 150 systolic and 90 diastolic.

2. The amount of albumin in the urine is never very great, varying before delivery between a fraction of a gram and 2 gm. per liter, although the lower figures are most usually observed. The albumin disappears during the puerperium, and the patient leaves the service either with no albumin at all, or with at the most 0.1 gm. per liter.

3. The outstanding characteristic is the fact that in subsequent pregnancies, the patient's condition does not become aggravated, and she is as well as, or better than, in the preceding pregnancy.

4. The blood chemistry, as well as the urine chemistry, reveals nothing abnormal.

That the number of pregnancies through which the individual may go plays any rôle in the development of this entity is very doubtful, for the reason that we observe it particularly in primiparas although occasionally in all degrees of multiparas. Moreover, this type of kidney does not seem to be permanently injured by pregnancy. As the woman approaches term a certain amount of albumin may pass through the glomerular membrane, the blood pressure becomes elevated, and some edema exists. With regard to the latter point, it is interesting to note that in subsequent pregnancies there is either no edema or at the most a slighter degree than before.

It is well known that in a healthy person, under normal conditions, all of the glomeruli are not functioning at capacity at any one time, and it has been estimated that there is usually a margin of safety which approaches 50 per cent. In other words, there is a decided kidney reserve which may be called into play. It seems reasonable to suppose that in certain individuals this kidney reserve may be greatly decreased due either to congenital causes or to such factors as may have lessened the number of functioning glomeruli without producing a chronic nephritis. As we have seen in another group of cases, the strain of pregnancy always aggravates a chronic nephritis, so that later the kidneys are less well prepared to stand the strain of subsequent pregnancies. In the type of kidney under consideration this is not the case. All we can say is that the kidney reserve seems to be too low to meet the extra demands of pregnancy, as is manifested by the passage of a certain amount of albumin through the glomerular epithelium and by a moderate elevation of blood pressure, and that these manifestations usually disappear completely within two weeks after delivery. Furthermore, the kidney substance does not seem to have been injured by the pregnancy and the kidney reserve is certainly not lower for subsequent

pregnancies. Such kidneys appear to be quite capable of functioning adequately while the woman is not pregnant, as well as for her and her fetus up to about the eighth or ninth month of pregnancy, when manifestations of the low reserve begin to make their appearance.

Before presenting studies on cases of low reserve kidney, we should like to state that this term has been criticized on the basis that it is vague terminology and that placing responsibility upon the kidney primarily appears misleading and "to indicate a limited and faulty conception of a process having broader implications."[7] Our conception of this group of patients may well be limited and faulty; however, we are just beginning to understand the intricate functions of the kidney, and are not even that far advanced in our knowledge regarding the etiology of certain types of hypertension. Volhard[2] stated "In the high pressure I see the cardinal problem of the entire renal pathology." There can be little doubt that the two factors mainly involved in hypertension are peripheral resistance and time-volume or cardiac force, and that of these the former is the more important, and may be due to not only an organic but also functional cause. One should bear in mind the fine blood pressure regulating mechanism of the organism. There is the powerful chemical regulation as well as the nervous one. It is conceivable that in what we have called low reserve kidney, the condition is more general, and the kidneys are not the important factor. However, it does not seem that, if it is a general, let us assume vascular, condition, the patient will, after conclusion of the involved pregnancy, proceed to have subsequent pregnancies during which there are no further or repeated signs of the general condition, that is, a reappearance of hypertension and albuminuria. It seems to us more logical to assume that the hypertension and albuminuria are dependent on a local kidney condition, which may not be present, at least to the same extent, in a subsequent pregnancy, or, if present to the same extent, the demands on the kidney in this subsequent pregnancy may be less or different. It seems, furthermore, logical to assume that even an essential hypertension, dependent upon arteriolar spasm, will not necessarily disappear after a pregnancy and what is even more important, not reappear in a subsequent pregnancy. The only other logical explanation, other than the assumption of such an entity as low reserve kidney, appears to be that in any given pregnancy there may be a substance or substances producing arteriolar spasm and so hypertension, but even then it is difficult to explain the albuminuria. However, in the light of our still incomplete knowledge of hypertensive disease as well as of kidney function, this may still be possible, and it is for that reason that we have stated above that our concept of the process involved may be limited and faulty.

Having admitted the inherent weakness in our argument and the possible pitfalls of such a limited concept as low reserve kidney to explain these cases, it seems to us that at present this is quibbling over

terms. It also is clear to us that this entity, as described above, has nothing in common with hypertensive vascular disease.

As albuminuria is a common finding in "low reserve kidney" patients, it is advisable that we consider some of the general aspects of proteinuria. Certain theories have been advanced to explain so-called "harmless albuminuria." Among these are lumbar lordosis, causing stasis of the renal veins, subnormal vascular development, and vasomotor instability. Elwyn[8] states that in all types of albuminuria, with or without renal damage, there is either injury due to a poison or toxin, or anoxemia, that is, a deficiency of oxygen supply, but that in all cases there is damage to the glomerular and capsular epithelium. Discussing the type of albuminuria seen in supposedly healthy individuals, Thorp and Wakefield[9] go so far as to say: "The burden of proof rests with those who do not consider it due to renal injury."

It is known that changes in the alkalinity of the blood can produce albuminuria, as it is found in acidosis, while alkali therapy decreases the amount of albuminuria. The albuminuria observed in nervous individuals may be due to localized areas of anoxemia, due to an instability of the vasomotor mechanism.

From these few general considerations of albuminuria, other than that accompanying definite and proven damage to the glomerulus or tubule or both, it would seem that this "harmless" albuminuria seen in low reserve kidney is most probably dependent on kidney changes per se, unless such general conditions as acidosis or vascular instability are the cause of it, and this latter assumption appears to us somewhat improbable as the condition is generally not accompanied by a nervous state or acidosis, and not even a more marked compensated alkali deficit than that seen in all normal pregnancies.[10]

We shall now consider 313 patients with low reserve kidney, who were admitted to the Lying-In Hospital during the period Sept. 1, 1932 to Dec. 31, 1933. We are not including any patients admitted after that period, in order that we may present a reasonably adequate follow-up study, as more than three years have elapsed since the last admission of the period studied.

TABLE I. INCIDENCE OF LOW RESERVE KIDNEY AND CHRONIC NEPHRITIS IN 3,352 FULL-TERM AND PREMATURE DELIVERIES

DIAGNOSIS	NO. OF CASES	INCIDENCE
Low reserve kidney	313	9.33%
Chronic nephritis	80	2.38%
Unclassified	58	1.73%

In 3,353 full-term and premature deliveries we find the number of low reserve kidney patients to be 313 or an incidence of about 9 per cent. In this group of patients there were no maternal deaths, while the incidence of infantile mortality was 5.91 per cent as compared with a clinic figure of 4.56 per cent, a difference of not much significance. It

should be stated that by "infantile mortality" we mean all deadborn or stillborn infants weighing over 1500 grams as well as those dying during the first two weeks following birth.

TABLE II. MATERNAL AND INFANTILE MORTALITY IN LOW RESERVE KIDNEY

MORTALITY	LOW RESERVE KIDNEY	TOTAL CLINIC DELIVERIES
Maternal	0	0.1 %
Infantile	5.91%	4.56%

The age incidence, as shown in Chart 1, is significant in that it is almost identical with the age incidence of the total hospital group

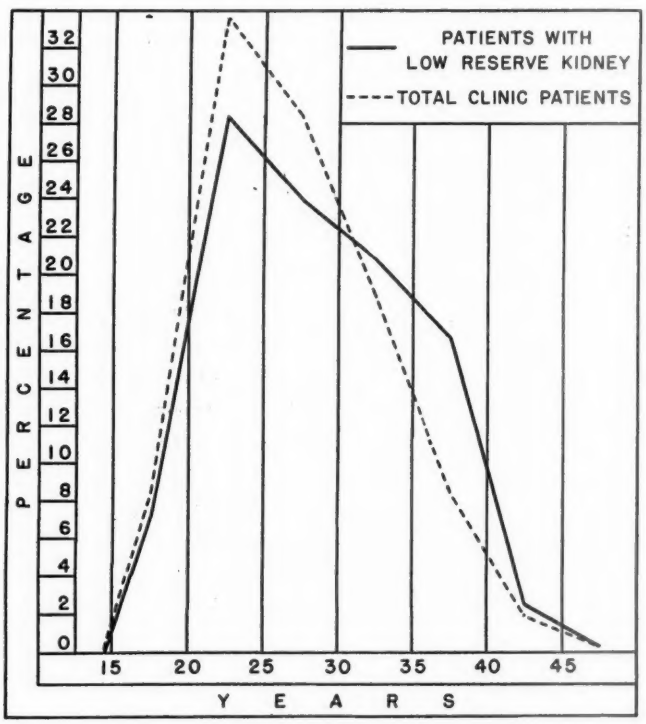

Chart 1.—Age incidence of low reserve kidney.

(clinic patients). There is no particular age group in which the incidence seems to be particularly high. When, however, this entity is considered in relation to parity we notice that it is a complication *particularly* of the first pregnancy. Chart 2 gives the parity incidence for 313 low reserve kidney cases, 80 chronic nephritics, and 2,619 nontoxemia patients in the group of 3,352 patients studied. We find that over half the cases of low reserve kidney occur in primiparas, whereas the clinic incidence of primiparas is only 45.8 per cent and that of chronic nephritis only 31.2 per cent. The curves in this chart are of further interest in that there is a marked relative increase in the cases of

chronic nephritis in subsequent pregnancies as compared with the total clinic, as well as the low reserve kidney parity incidence.

TABLE III. INCIDENCE OF COMPLICATIONS IN PATIENTS WITH LOW RESERVE KIDNEY

	PATIENTS WITH LOW RESERVE KIDNEY	TOTAL CLINIC PATIENTS
Complications:		
Cardiac disease	2.2%	3.07%
Pyelitis	1.5%	1.50%
Tuberculosis	0.3%	0.61%
Syphilis	1.2%	2.06%

Complications of pregnancy such as cardiac disease, pyelitis, tuberculosis, and syphilis apparently play no role in the etiology of low reserve kidney, as shown by Table III. Similarly, when we study previous

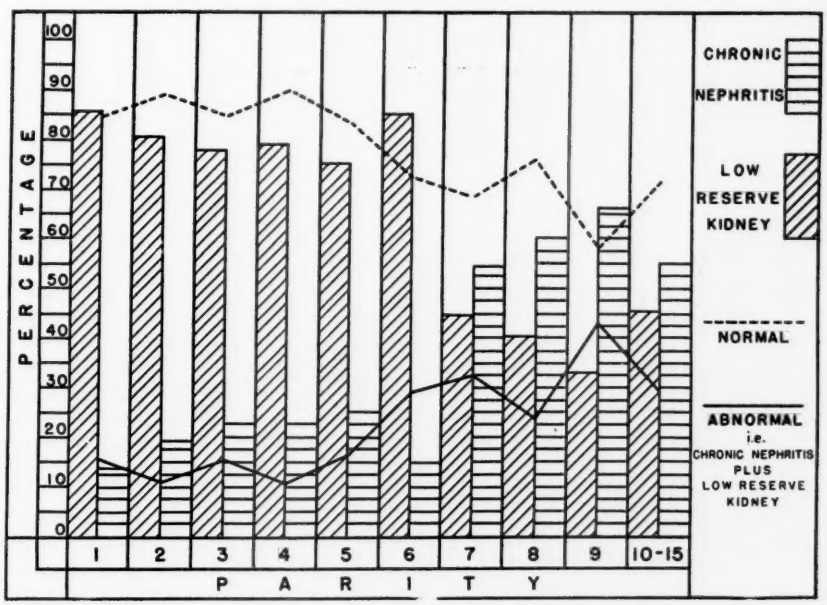

Chart 2.—Chronic nephritis and low reserve kidney in relation to parity.

diseases, as noted in the histories (Table IV), no correlation can be found between these and low reserve kidney, and this may also be said with regard to previous toxemia in an earlier pregnancy. Out of the total of 313 cases of low reserve kidney, only 14 had a history of toxemia in a previous pregnancy, 1 eclampsia, 4 chronic nephritis, and 9 high blood pressure, and it is extremely doubtful whether the previous diagnosis of chronic nephritis was correct as shown by Table V.

A study of the period of pregnancy at which the first sign of hypertension or albuminuria appears in these cases of low reserve kidney is of the utmost importance (Chart 3). It will be seen that the onset of these signs of low reserve kidney is mainly during the two last months of pregnancy, that is, from the thirty-second week to term. It never

TABLE IV. PREVIOUS DISEASE IN 313 PATIENTS WITH LOW RESERVE KIDNEY

PREVIOUS DISEASE	TOTAL CASES	NO FOLLOW-UP AFTER 1933 DELIVERY	AFTER ADEQUATE FOLLOW-UP	
			LOW RESERVE KIDNEY CORRECT DIAGNOSIS	LOW RESERVE KIDNEY NOW CORRECTED TO CHRONIC NEPHRITIS
Scarlet fever	25	13	12	0
Smallpox	1	1	-	-
Diphtheria	4	2	2	0
Typhoid fever	1	1	-	-
Chorea	2	-	2	0
Rheumatism	10	4	5	1
Nephritis	7	5	2	0
		26	23	1
Total	50		50	

TABLE V. PREVIOUS TOXEMIA IN 313 PATIENTS WITH LOW RESERVE KIDNEY

TOXEMIA DIAGNOSIS IN PREVIOUS PREGNANCIES	TOTAL CASES	NO FOLLOW-UP AFTER 1933 DELIVERY	AFTER ADEQUATE FOLLOW-UP	
			LOW RESERVE KIDNEY CORRECT DIAGNOSIS	LOW RESERVE KIDNEY NOW CORRECTED TO CHRONIC NEPHRITIS
Eclampsia	1	-	1	0
Nephritis, chronic	4	1	1	2
High blood pressure	9	3	4	2
		4	6	4
Total	14		14	

makes its appearance in the first half of pregnancy, and in this respect differs from chronic nephritis.

We now come to the most important part of this study, which is the behavior of the cases in subsequent pregnancies. Of the 313 patients with low reserve kidney diagnosis in a pregnancy during the period Sept. 1, 1932 to Dec. 31, 1933, we have 55 women returning to our hospital in a subsequent pregnancy. These 55 patients were carefully studied and a detailed "toxemia chart," similar to Chart 5, maintained for each. A survey of Chart 4 shows that of these 55 patients, who had the signs of a low reserve kidney in a previous pregnancy, 35 or 63.6 per cent, had no hypertension, no albuminuria, no edema and no symptoms indicative of toxemia, in the subsequent pregnancy. This observation, as we have said, is of the utmost significance. If this particular toxemia is dependent upon vascular changes, either organic (arteriolosclerosis), nervous, constitutional (familial) or chemical in origin, one would suppose that all 55 patients should manifest at least such toxemic signs in a subsequent pregnancy, or perhaps those of actual kidney involvement (chronic nephritis of one or other type). The only other explanation for this striking observation, it seems to us, is that the original diagnosis of low reserve kidney should have been what Kellogg

calls preeclampsia Grade I. In this group of patients, however, we have at no time observed the other signs, symptoms and blood chemical changes described by Stander and Cadden[11] in 40 patients with preeclampsia. This, of course, may be partially explained on the basis of severity, and we are not prepared at present to state categorically that Kellogg's classification[12] is at error in this respect. Much further investigative work is needed before a final decision on this entity can be made. It is our present opinion, however, that from the clinical course, the behavior of the blood pressure and albuminuria, the blood chemistry

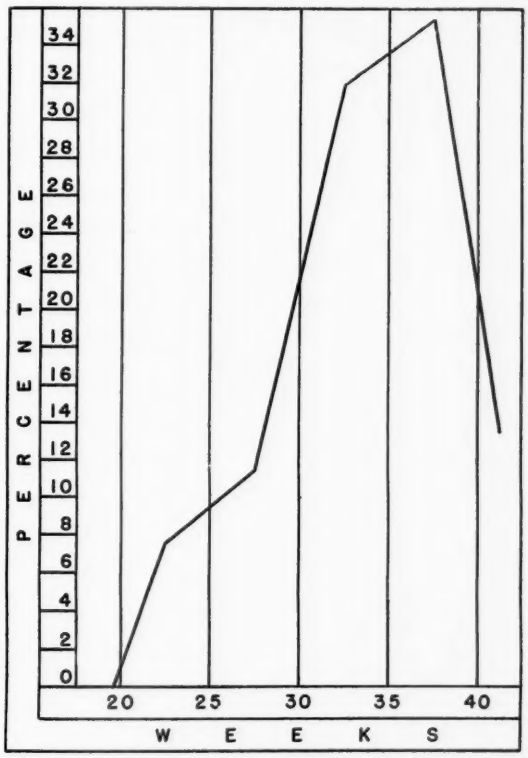

Chart 3.—Onset of toxemia in relation to duration of pregnancy in 313 cases of low reserve kidney.

and the eye-findings, the assumption of a low reserve kidney fits the picture better than that of a mild type of preeclampsia. Nevertheless, at present this is in great part only a difference in terminology, as the cause of the disease eclampsia, and its milder form, preeclampsia, is not yet known. But of the greatest importance, is the fact that this follow-up study in a subsequent pregnancy, indicates, and we believe, quite clearly, that the "low reserve kidney" findings cannot be explained on the basis of a general vascular disease with hypertension, as suggested by Herrick and Tillman.[7]

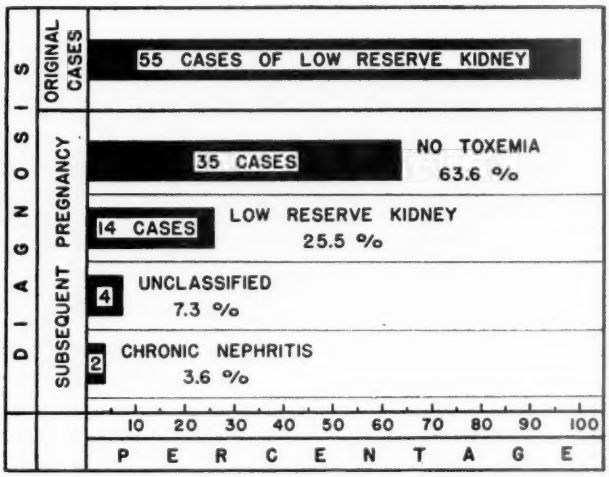

Chart 4.—Diagnosis in subsequent pregnancy in 55 cases of low reserve kidney.

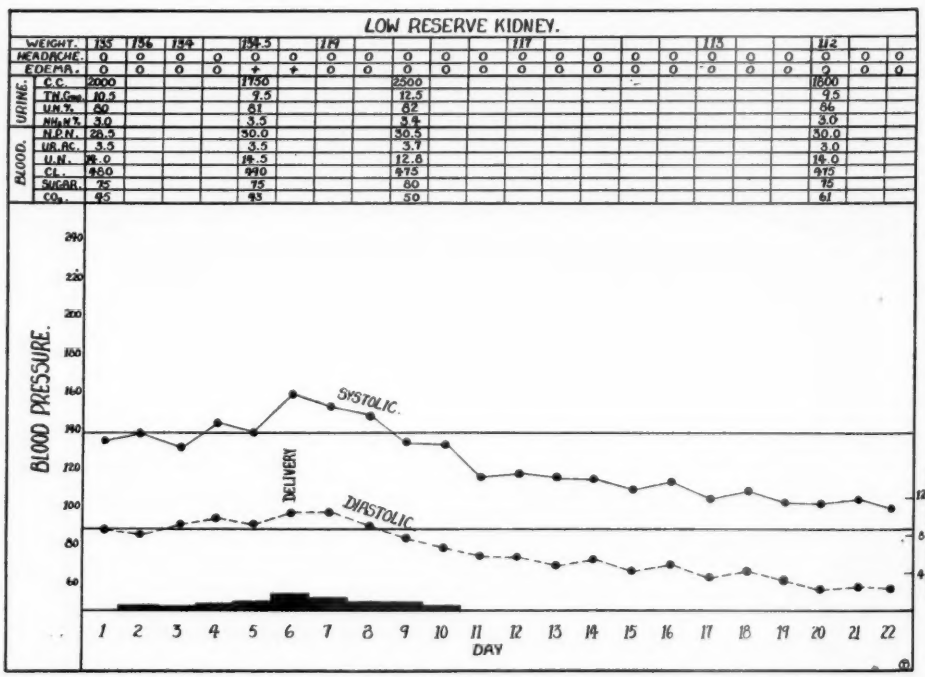

Chart 5.—Behavior of systolic and diastolic pressure, albuminuria and urine and blood chemistry in low reserve kidney. (From Stander, H. J.; *Williams Obstetrics*, New York, D. Appleton-Century Company, ed. 7, 1936.)

In Table VI is listed the treatment as to delivery, pursued in the original 313 cases of low reserve kidney. It will be seen that in no case was pregnancy terminated because of the toxemia, signifying a most conservative attitude, quite different from the one we follow in the treatment of chronic nephritis and to some extent of preeclampsia.

TABLE VI. TREATMENT IN LOW RESERVE KIDNEY

Type of Delivery:			
Spontaneous deliveries			228
	INDICATION		
OPERATIVE DELIVERIES	FOR TOXEMIA	OTHER CAUSES	TOTAL
Insertion of bougie for induction of labor	4		4
Cesarean section		11	11
Version and extraction		3	3
Breech extraction		9	9
Forceps	5	53	58
Grand total			85

Incidence of operative deliveries = 27.15%
Total clinic incidence of operative deliveries = 21.95%

In the last table (VII) are listed 35 patients in whom we were unable to make a definite diagnosis during one pregnancy but were able to study these patients in a subsequent pregnancy. Of these 35 patients, 21, or 60 per cent, showed chronic nephritis in the subsequent pregnancy

TABLE VII. FINAL DIAGNOSIS IN GROUP OF 35 UNCLASSIFIED TOXEMIAS AFTER FOLLOW-UP STUDY

TOXEMIA	NUMBER OF CASES	INCIDENCE
Chronic nephritis	21	60.0%
Low reserve kidney	7	20.0%
No toxemia	2	5.7%
Remained unclassified	5	14.3%

and only 7 or 20 per cent, low reserve kidney. From this it may be concluded that we are too hesitant to make the diagnosis of chronic nephritis, and it would serve the patient's interest better if we were more rigid in the process of exclusion from the chronic nephritis group.

Finally, we wish to discuss briefly the diagnosis of "chronic nephritis." In the earlier part of this paper we mentioned the various types of nephritis and their respective etiologic factors. We are fully aware that many cases we group as "chronic nephritis" actually belong in the category of vascular hypertensive disease, without perhaps as yet actual kidney involvement. We purposely put them in the nephritic group, for the reason that we consider their condition far more serious than that of low reserve kidney, and that hypertensive disease, of whatever origin, either benign or malignant, sooner or later reveals kidney involvement, unless the patient succumbs from cardiac or apoplexy death before the signs of kidney involvement become apparent. From an

academic point of view it is well that we attempt, in each case falling in the large group "chronic nephritis," to establish the type of nephritis or the form of vascular disease, and this is done in every case in our hospital. Past history, clinical course, symptomatology, blood pressure, and albuminuria charts, repeated urea clearance, phenolsulphonephthalein and dilution and concentration kidney function tests, microscopic examination of the urine, Addis' cell count, repeated blood and urine chemistry, repeated eye-ground examinations, and the observation of edema, are all of utmost importance in each case. We have so studied all our patients with signs or symptoms of toxemia, and have in many instances been able to diagnose the *type* of kidney or vascular involvement. However, from a practical standpoint we believe it is far more important to know whether the patient belongs in this general vascular-renal group, which we label "chronic nephritis" rather than to know the exact entity. We must know that the condition is not simply a low reserve kidney, or the more serious preeclampsia, but that it is a "chronic nephritis," as our treatment then is greatly altered.[3] We would not interrupt a pregnancy for low reserve kidney, we would at times interrupt a pregnancy for preeclampsia, but we would never sterilize a patient in whom the diagnosis is preeclampsia, a procedure we often follow in chronic nephritis.

SUMMARY

We have presented a description of the present theories relating to the functions of the kidneys, and have attempted to indicate how these functions are affected in pathologic conditions. We have discussed the various types of nephritides, as well as general vascular conditions associated with hypertension and leading later to renal involvement.

A follow-up study of 313 patients with low reserve kidney is presented. The evidence, as revealed in subsequent pregnancies, strongly supports the concept of low reserve kidney and speaks against a general vascular disease or condition, whether of sclerotic, nervous, chemical, or familial origin, as the basis for this entity. Furthermore, it appears to be an entity distinct from any of the known nephritides, whether of the hemorrhagic, degenerative, or sclerotic type. It also does not seem to fall into the category of a mild preeclampsia. That this entity cannot very well be explained on the basis of a general vascular condition is the opinion, expressed in personal communications, of both Van Slyke and Marshall. The former has had an opportunity, in his nephritic service in the Rockefeller Institute Hospital to study various phases of hypertension and of the different forms of nephritis, while the latter has been responsible for an important part of our newer knowledge relating to the functions of the kidney. These investigators concur with us in the view that the concept of low reserve kidney appears to be sound. It must be

pointed out, however, that it is not our opinion that the existence of such an entity has been proved and much further investigative work, especially upon maximum excretion capacity, is needed before we can prove or disprove this theory. Richards and Landis have given us some very valuable suggestions along these lines and we hope, in the near future, to be able to follow these.

We believe that in this group of low reserve kidney patients, one or other of the factors influencing glomerular and perhaps also tubular function, may be involved. Such factors are rate of blood flow through the kidney, permeability of glomerular membrane as well as tubular walls, extent of filtration surface (glomerular), and perhaps also the effective filtration pressure. Unfortunately, very little is known as to the factors influencing tubular reabsorption, except the factor of time of contact of the glomerular filtrate with the tubular epithelium. That the involvement of one or other or combination of these factors, bringing about the signs of this entity (low reserve kidney), is dependent on inherent or inherited differences from the normal, or on a specific pregnancy condition such as hormonal or chemical or vegetative nervous, cannot at present be decided. Pressure on the renal veins or kidney pedicle, as suggested by Marshall, in a personal communication, should also be borne in mind as a cause of the albuminuria, although this may not explain the hypertension. We have discussed at some length the nervous reflex mechanism, as well as the other factors influencing blood flow through the kidney.

CONCLUSIONS

1. The concept of "low reserve kidney" indicates that the ability to meet ordinary excretory demands is retained, while competence to meet extraordinary demands is impaired.

2. Such decrease in reserve may result from a diminution in functional capacity or from actual structural change resulting in a decrease in the number of functioning units.

3. The concept of "low reserve kidney" appears to us to be sound from the viewpoint of kidney physiology as well as from that of clinical observation, although we fully realize that much further investigation is needed, before the existence of such an entity is either proved or disproved.

4. In approximately one-half of our cases of low reserve kidney there is no recurrence of hypertension or albuminuria in subsequent pregnancies.

5. We do not believe that the assumption of a general condition, such as hypertensive disease, or a general vascular disease of whatever origin, nervous, familial, sclerotic, chemical or hormonal, explains this group of low reserve kidney patients, as in such event, there should be a return

or continuation of the signs in all subsequent pregnancies. A temporary circulatory disturbance may conceivably account for the signs of low reserve kidney.

6. We are of the opinion that with our present inadequate knowledge of kidney physiology, as well as of hypertensive disease, the term "low reserve kidney," although perhaps not accurate as indicating the real etiology, best describes the group of patients under discussion, and, instead of being vague and narrow in that it focuses attention on the kidney, serves a useful purpose for this very reason. In this connection we have particularly in mind the recent work on so-called "harmless albuminuria," and think that, in the interest of the patient, attention should be directed to the kidney.

7. It cannot be clearly shown that low reserve kidney is not a very mild form of preeclampsia, although we believe the evidence, and particularly the blood chemistry, is against such an assumption.

8. Low reserve kidney is distinct and different from all the known nephritides, whether hemorrhagic, sclerotic or degenerative.

9. Low reserve kidney appears most frequently in the young woman with her *first* pregnancy, as shown by Peckham and Stout.[13]

10. Low reserve kidney appears only in the last month or two of pregnancy, and reveals itself by a mild hypertension and albuminuria and sometimes slight edema.

11. Kidney function tests and blood and urine constituents are normal in this condition.

12. The treatment for low reserve kidney is conservative as distinct from that in proved chronic nephritis.

13. The most common error in the diagnosis of low reserve kidney consists in designating cases of chronic nephritis or perhaps general vascular disease, as low reserve kidney. The incidence of low reserve kidney is, therefore, lower than we originally indicated, and accounts for probably only about one-third, or less, of all toxemias of pregnancy.

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LEUCOPLAKIA, LEUCOKERATOSIS, AND CARCINOMA OF THE CERVIX*

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A QUESTION which has been discussed repeatedly in the past few years is the relationship between leucoplakia and carcinoma. Does the leucoplakia of the cervix always, or at least in a significant number of cases undergo carcinomatous changes? A great deal of work, which can hardly be overlooked, has been done in attempting to answer this question. Frequently the problem is confused by the question as to whether the leucoplakia is not merely a precarcinomatous stage of the portio. The entire situation is thrown into further confusion by the improper use of the word "precancerous" or "precarcinomatous." Some authors use the word to describe pathologic changes which *invariably* lead to carcinoma while others use it to describe changes that *might* lead to carcinoma.

It must be pointed out emphatically that leucoplakia does not describe a definite and specific disease and that it presents neither a definite clinical entity, nor a well-defined pathologic, anatomic, or histologic picture. For this reason, Robert Meyer, in his contribution to *Henke-Lubarsch's Handbook* (**7**: No. 1) refused to accept the usage of "leucoplakia" in the pathologic-anatomic sense. The word "leucoplakia" does nothing but convey the optic impression which the examiner gets either with the naked eye, or by means of a colposcopic examination; it describes a bright white patch. However, various changes of the mucous membranes lead to the formation of similar white patches. It is impossible to determine with the naked eye, or even with magnifying instruments, the type of pathologic changes which underlie the leucoplakia. Structural changes of the mucous membranes cause a reflection of light, thus forming white spots. This is only one part of the pathologic change involved, one which can be recognized with the naked eye. A part of a pathologic process is called a symptom; the word leucoplakia is used to describe an optic impression, it is nonspecific and may occur in various diseases of the mucosa. There are symptoms which are specific for certain diseases and with the appearance of these symptoms a diagnosis is definitely established. Leucoplakia definitely does not belong to this group of symptoms. The question as to whether leucoplakia is malignant or not can only be understood properly if we consider all the various changes of the portio mucosa, which fall into the optical group of leucoplakia. Since we are confronted with various

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changes, the question cannot be answered unless we discuss in detail every process which is grouped under leucoplakia. In the literature there are cases of leucoplakia described which were already carcinomatous when first observed (Kolevajev, Franquè, Hinselmann); cases of leucoplakia which developed into carcinoma after a long period of time (Geller, Esser, Labadie, Puccioni), and finally cases which never offered any proof of malignant degeneration even after years of close observation (Philipp and Schäfer, Rogge). These reports appear contradictory. The various observers have described different diseases which have only the external appearance in common. Observations can only be of value where an exact histologic description is given of the mucosal changes which led to the histopathologic diagnosis of leucoplakia. Where such microscopic descriptions are not given, the observations are of limited value because of the nonspecific character of leucoplakia as a symptom. "Leucoplakia" should no longer be used as a misnomer nor should there arise the question of "leucoplakia" degenerating into carcinoma. An analogous question would be: Can icterus develop into carcinoma? There are cases of icterus which have nothing in common with carcinoma formation, hemolytic icterus for example. Another group of icterus, the obstructive type, may lead secondarily to carcinoma. Finally icterus may develop as a symptom of carcinoma of the liver or gallbladder. Icterus is neither a disease nor a diagnosis, but a symptom common to several diseases; its relationship to the development of carcinoma is manifold. The relationship between leucoplakia and carcinoma is similar. In order to avoid confusion and to understand properly the relationship between leucoplakia and carcinoma, we must discard the use of the word as a diagnosis and use it as a symptomatic description only; the diagnosis of the affection that appears as leucoplakia should be made on histologic findings only.

Clinically, the word leucoplakia does not convey a definite, characteristic picture. They vary in size, shade and may have a well, or poorly defined borderline. Some appear as white spots on the surface of a reddish portio and are easily recognized. There are various shades of leucoplakias, from the pure white to a shade slightly brighter than the surrounding mucosa, so that the color difference can only be discerned on close examination with optimal light. Leucoplakias may be set off from the surrounding area by a sharp, linear borderline or they may merge gradually into the surrounding darker area. Other characteristics which may or may not be present are: niveau differences, or a dull surface. These manifold differences between the various forms of leucoplakia can frequently be recognized with the naked eye, to say nothing about a colposcopic examination. On the other hand, leucoplakias which differ only slightly in color from the surrounding normal tissue may be easily overlooked during a hasty, routine examination.

In such cases iodine is very useful. Iodine application can serve to increase the number of clinically diagnosed leucoplakias by making visible the lesions which would otherwise escape the naked eye. Borderline cases, which cannot be or are hardly seen with the naked eye will be referred to as latent leucoplakias. The purpose of the iodine application is to make the grossly visible leucoplakia appear clearer and to make the latent leucoplakia visible to the naked eye. The iodine fulfills this function so well that the latent leucoplakia appears better defined and sharper than grossly visible areas of leucoplakia which were not treated with iodine. If there is a beginning carcinoma among the latent leucoplakia, the iodine will reveal its presence even if other clinical methods failed. Long clinical experience has shown that the number of latent leucoplakias diagnosed with the aid of iodine by far exceeds the number of grossly visible leucoplakias. Furthermore, all grossly visible leucoplakias are iodine negative, they appear as white, sharply-defined areas. On the other hand a large part of leucoplakias which can only be diagnosed with the aid of iodine are invisible to the naked eye. In this paper the word leucoplakia will be used to designate those mucosal changes of the portio which cause white patches to be visualized when aqueous Lugol's solution is applied. Normally the mucosa of the portio and vagina turns brown when Lugol's solution is applied, because of the glycogen content of the surface epithelium. In the absence of glycogen, there is no brown coloration. This may first of all happen when the normal, glycogen-containing epithelium is removed through trauma, as it may occur in the course of a gynecologic examination. These traumatized areas are identified by their sharp, ragged edges and by the partly attached traumatized surface epithelium. Their niveau is lower than that of the surrounding area. They appear as reddish white light spots when painted with Lugol's and regenerate within several days. The regenerating epithelium appears as an iodine-negative leucoplakia as long as it is glycogen free. These regenerative latent leucoplakias, which can only be seen after iodine application, have a smooth mirror-like surface and appear sunken in. Exact observation shows that they disappear in several days. The traumatic and regenerative leucoplakias do not lead to any permanent pathologic changes and are of no special interest here. The loss of glycogen-containing surface cells is due to extrinsic factors. The loss of glycogen-storing properties of the epithelium, as encountered in carcinoma and cornification, however, mostly is due to intrinsic factors. Cornification and carcinoma give rise to manifest, or latent leucoplakias. This observation proves that there are leucoplakias which are definitely carcinomas, or at least carcinoid or carcinomatous epithelium (Beläge). The exact nomenclature is neither of theoretical nor of practical importance. Leucoplakias, which show definite carcinomatous changes and fulfill all of Schottlander's and Kermauner's criteria for carcinom-

atous "Beläge" are admitted as "potential" carcinomas, even by observers who are diagnosing carcinoma by invasion only (Franqué, Freedmann, Ries, Rogge, Stone). If there is invasive growth in addition, then it will convince even the most critical observer of its malignancy. The only fact of importance is that the superficial carcinomatous layer, which sometimes resembles a leucoplakia, may retain its superficial character for months or years before becoming invasive. The answer to the question whether such leucoplakias can become malignant is that they *are* already malignant.

Cornification is another process which destroys the glycogen-storing properties of the portio epithelium. Thompson proposed to use the word leucoplakia for changes of epithelium only that are of the type of abnormal cornification. The ideally normal portio epithelium, as described by Hinselmann (Zentralbl. Gynäk. 57: 2402, 1933, Fig. 1); and by Schiller (Zentralbl. Gynäk. 57: 418, 1933, Fig. 2), contains in its surface layers, rhomboid, or flat cells. When stained with the usual acid stains, these cells show no protoplasma but empty chambers. Special staining with Best's alkaline karmin, or with iodine, reveals glycogen granules in these superficial cells. The glycogen content of these cells depends to a certain extent on endocrine secretions. It is regulated by folliculin; the glycogen content is increased during pregnancy, or in the premenstrual period. Folliculin, however, is not the only factor involved. Under otherwise normal circumstances there is sufficient glycogen in the portio epithelium of castrated or postclimacteric women.

Physiologically, the vaginal and portio epithelium remain at a level, which the normally cornified skin epithelium goes through in the course of its embryonic development. Up to the fifth fetal month the surface epithelium of skin contains glycogen granules; subsequently, cornification takes place, as Ciliacus pointed out, at first on the palm and sole. Vaginal, portio, and esophageal epithelium remain in the "glycogen-storing" stage, but the possibility of prosoplastic cornification is always present in these epithelia. Traces of cornification in the epithelium of the esophagus are not infrequent, as *Stieve* has shown. The portio epithelium always possess a latent potency for prosoplastic cornification. Adequate stimuli will awaken this latency. These stimuli may be external, such as constant pressure, dryness, or chronic inflammations; syphilis. Furthermore there may be areas which have a pathologic tendency toward cornification, without any known external or internal stimuli being present. In the field of skin ichthyosis there is a good example of this type of cornification.

The glycogen-storing epithelium of the portio appears transparent and has a smooth (mirror-like) surface. The cornified epithelium, however, appears opaque and bright because of the light reflection; the surface is dull and uneven because of desquamation of cornified cells.

The cornification and desquamation produce bright, sometimes even white patches against a darker background. In other words there is a typical picture of leucoplakia. Leucoplakias formed through cornification being different from the viewpoint of histopathology, from changes in epithelium through trauma or carcinomatous growths should be differentiated in terminology. This can be done easily by borrowing a term from laryngology where similar changes are called leucokeratosis (Fein, Identity of Leucokeratosis buccalis and laryngis, Monatschr. f. Ohrenheilk. 5: 37).

Cornification may be incomplete or complete. The former is characterized by the absence of a keratohyaline layer, the persistence of the horn-layer nuclei and is called *parakeratosis.* The latter is characterized by a keratohyaline layer and a completely hornified layer without cell nuclei; this is called *keratosis.* Excessive hornification is termed *hyperkeratosis.* Applying this terminology to analogous changes in the portio epithelium one may speak of leucoparakeratosis, leucokeratosis and leucohyperkeratosis. Leucohyperkeratosis is merely a higher degree of leucokeratosis and the division line between the two is more or less arbitrary. For the skin a certain degree of cornification is physiologic, so that one cannot regard keratosis of the skin as pathologic; a hyperkeratosis, however is pathologic.

Parakeratosis is an incomplete form of cornification. Throughout this paper the word leucokeratosis will be used to denote cornification in general and will be divided into two subgroups.

1. The incomplete cornification, or leucoparakeratosis; this is characterized by the absence of keratohyalin and presence of nuclei in the horn layer.

2. The complete cornification, in the case of the cervix it is an excessive cornification—leucohyperkeratosis. Here we have a keratohyaline layer but no nuclei in the horn layer. The leucohyperkeratosis develops from the leucoparakeratosis and nearly always has a marginal zone of leucoparakeratosis. The leucoparakeratosis develops from normal epithelium. It merges gradually from the normal, glycogen-containing epithelium; this gives it a blurred borderline when iodine is applied. Occasionally one finds leucokeratosis with sharp borderlines. On cross-section, however, these borderlines are perpendicular as contrasted with the oblique borderlines of carcinomatous layers. Histologically, there is an abrupt change in the type of epithelium; grossly there is a sharp linear border between white and brown coloration after iodine application. (Schauenstein, Arch. f. Gynäk. 85: 1908, Plate 15, Fig. 4; Hinselmann, Ztschr. f. Geburtsh. u. Gynäk. 94: 164, 1929, Fig. 1; Haselhorst, Ztschr. f. Geburtsh. u. Gynäk. 98: 1930, Fig. 5; Schiller, Arch. f. Gynäk. 133: 257, 1928, Figs. 3, 5, 16.)

The oft-repeated question whether leucoplakia of the portio is carcinomatous or precarcinomatous will not be understood properly unless it is divided into its two component parts. The first part of this question, whether the carcinomatous layers ("Beläge") are merely *precarcinomatous* or already carcinomas, is of little theoretical and of no practical value. The second part of the question is: are the leuco-

keratoses, which are not carcinomatous as yet, to be regarded as precarcinomatous in the sense that they *always* or only *occasionally* develop into carcinomas?

In answering this question it is advisable to classify leucokeratosis according to etiology. The syphilitic leucokeratosis is hardly worth mentioning because there are only a few cases encountered, not enough to draw any conclusions. Syphilis of the cervix is very rare and plays a small rôle in our material. There are only a few cases mentioned in the literature (l'Espérance, Haselhorst, Verdalle); among his 28 cases of leucoplakia, Kolegajev found one syphilitic only. Hinselmann reported only a few cases of syphilitic leucoplakias (Monatschr. f. Geburtsh. u. Gynäk. 77: 1927, Arch. f. Gynäk. 130: 212, 1927, Zentralbl. f. Gynäk. 52: 282, 1928). A few cases of syphilitic leucoplakias were reported by Gellhorn. In my series of cases, however, they were very rare. Over a period of many years I occasionally only found a leucoplakia in a patient with positive Wassermann test. The relative number of these cases is so small that it might have been a coincidence only to find a leucoplakia with a positive Wassermann. Definite causal relationship between the two could be proved by the disappearance of the leucoplakia and negative serology after antisyphilitic treatment. This actually happened in one of my cases, but one case is not conclusive.

The following is a report of two cases of leucohyperkeratosis with positive Wassermann, without descensus or prolapse.

CASE 1.—J. F., aged forty-one years. Menstruation began at sixteen, regular, every four weeks, lasting three or four days, last menstrual period three weeks ago. Patient complained of low back pain of three months' duration. This pain radiated to the left and was aggravated during menstruation. Gynecologic findings: Uterus about the size of a fist, irregular, hard, movable; adnexa and parametria negative. On the anterior portio lip there were several, small, fairly well-demarcated areas of leucoplakia. Posterior portio lip was badly eroded. Wassermann was positive. In view of the small fibroid and the patient's age, sterilization with x-ray was resorted to. Biopsy of a small wedge-shaped piece of tissue from the edge of a leucoplakic area showed fairly thickened epithelium, which changed from parakeratosis to typical hyperkeratosis with a wide, keratohyalin layer; the superficial, nuclei-free horn layer was nearly as thick as the rest of the epithelium. There was a marked, diffuse, inflammatory infiltration of the papillary bodies; this infiltration was also to be found where there was little or no cornification.

CASE 2.—P. Z., aged fifty years. Menstruation began at seventeen, every four weeks, profuse flow. One parturition, no abortions; pelvic inflammatory disease two years ago. Patient complained of severe pain of two weeks' duration, in the sacrum and left adnexa. Gynecologic findings: Uterus somewhat enlarged, not definitely made out, tenderness on motion; there was a small cervical polyp about the size of a pea presenting at the external os. Application of Lugol's revealed a sharply-defined leucoplakic area on the posterior lip. Microscopic examination showed extremely thickened and cornified epithelium. Patient refused treatment; follow-up examination ten months later showed no change in the leucoplakia. An interesting observation was that the surface of the leucoplakia was flat and did not follow the curve of the portio. Microscopic examination showed marked parakeratosis with beginning hyperkeratosis.

Does the leucokeratosis caused by dryness of prolapse tend to develop into carcinoma? This question can be answered by reviewing the incidence of carcinomas in cases with prolapsed uteri. In 1928 Högler published his work on the relationship between carcinoma and prolapse, since then the observations of other workers appeared in the literature (Gunsett and Ritter, Heidler, Kraul, Boukalik, Tourneux, Natale, Emmert and Taussig, Geller, etc.). The consensus of opinion is that the combination of carcinoma and prolapse is rather rare; a prolapsed uterus has less tendency to carcinomatous growth than a uterus in normal position. Indirectly, through secondary changes of the epithelium, the prolapse offers a certain degree of protection against carcinoma. It is certain that the highly differentiated, cornified and dried-out epithelium has less tendency toward malignant degeneration than the normal epithelium. Skin malignancy of the palm or sole is extremely rare in spite of progressed cornification and constant exposure

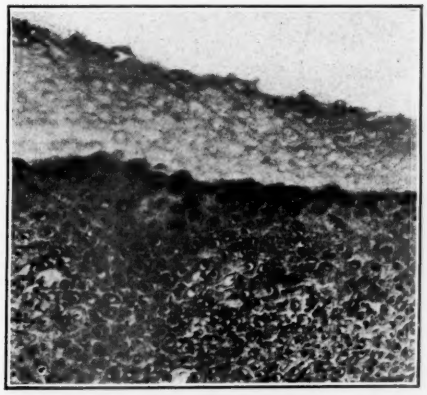

Fig. 1.—Syphilitic leucoplakia (Case 2); a well-developed keratohyalin layer with a thick superficial horn layer. (×140.)

to pressure of these two areas. On the other hand carcinomas of the skin are not rare where chronic irritation, arsenic poisoning for example, causes a hyperkeratosis. Neither the mechanical irritation, nor the cornification, as such, is of any significance in the development of carcinoma of the skin. The same observation holds true for the carcinoma of the cervix. The small percentage of carcinomas in prolapsed uteri with resulting cornification supports this observation.

Since neither the syphilitic leucoplakia, nor the leucoplakia caused by prolapse plays an important rôle in the etiology of portio carcinoma, we will pass on to a third group of leucoplakia, the spontaneous or autonomous type for which there is no apparent cause. This group of leucoplakia is of special interest because of its spontaneous character, comparative frequency, obscure etiology, and its possible causal relationship to carcinoma.

According to some authors the intermediate cornification, or the three-layer epithelium of the portio and vagina, is a result of premenstrual

changes. The author was able to show that this condition very frequently can be found independent of the menstrual cycle and occurs in postclimacteric as well as in castrated women. The epithelium next to the region of advanced carcinomas also shows this characteristic division into three layers. This epithelial change could be interpreted as a reaction to the carcinoma. It has been shown, however, that even the smallest beginning carcinomas originate in such a three-layer epithelium. In other words, the primary site of the carcinoma is prosoplastically, highly differentiated and has a predisposition to cornification prior to the beginning of carcinoma growth. The explanation to the apparent contradiction, between this statement and the foregoing conclusion concerning leucoplakia cornification in prolapsed uteri and carcinoma incidence, is to be found in the difference between the two types of cornification. The cornification in the prolapsed uterus is a physiologic reaction against drying. The cornification referred to as the third group, when occurring in a normally placed uterus, is a spontaneous, prosoplastic change; a sort of automatic hyperactivity of the epithelium, or due to the influence of hormone (folliculine).*

Vitamin-lack is the cause of a special type of cornification. It was recently discovered and was experimentally investigated in rats and mice (Evans, Reis and Perényi, Adler and Böttink, Wohlbach and Howe, Goldblatt and Benischek, Green and Mellanby, Euler and Mahnberg). It is a diffuse type of cornification and affects not only the vaginal mucosa but also that of the respiratory tract. In the animal it never causes a circumscribed cornification. The importance of this type of cornification in the human being is still unknown. It is possible that a local prosoplastic tendency to cornification is activated by a diet poor in vitamins. It is unlikely that there is any relationship between vitamin lack and the chronic leucoplakia of the portio, which even recurs after removal. In a recently published excellent paper, Swift demonstrated the relationship between achlorhydria on one side and hyperkeratosis and kraurosis of the vulva on the other side.

Do the more advanced types of cornification, as exemplified clinically by leucopara- and leucohyperkeratosis, also tend towards malignant degeneration? The reviewed literature does not answer this question satisfactorily. Cases of carcinomas developing from leucoplakia have been reported. However, the microscopic descriptions in all these cases either do not present exact histologic pictures of the leucoplakia or do not exclude the possibility of a primary carcinomatous surface epithelium. Only the case Alpers reported by Hinselmann serves to establish a relationship between carcinoma and noncarcinomatous leuco-

*According to Schwimmer, the leucoplakias of the mouth are caused by chronic inflammations (syphilis), or by chronic irritations (tobaccos, etc.). Brofeldt has the same point of view in regards to the leucoplakias of the mucosa of the lips. In an excellent work, recently published, Bencini has shown the autonomous character of the leucoplakia of the kidney pelvis.

plakia; but in this case there is no evidence that the area of leucoplakia primarily was a leucokeratosis.

According to the degree of cornification one can divide the leucokeratoses into two groups. In the first group the iodine test reveals extensive, confluent, irregularly shaped areas on the portio mucosa. These areas are brighter than the normal mucosa: they rarely appear white. Their colors generally range from dark yellow to light brown. Each area may have several shades. Microscopic examination shows slight parakeratosis with occasional remnants of glycogen-containing cells. Repeated examinations show that these areas of leucoplakia are very unstable. They disappear, sometimes within a few days and appear again with a different shade and outline. This type of areas of leucoplakia has no relationship with the portio carcinoma; it differs from the rare but stable carcinomatous leucoplakia by its flighty and inconstant character and its relative frequency as compared with the relative infrequency of portio carcinoma.

The second group consists of the true leucohyperkeratoses. It is distinctly apart from the syphilitic leucohyperkeratosis or the leucohyperkeratosis of prolapse. Clinical examination of the portio shows small, sharply outlined, white spots with linear borders and dull surfaces. Iodine application sets them off as bright, white spots from the surrounding, dark brown normal epithelium. These areas of leucoplakia examined with the naked eye greatly resemble the carcinomatous layers. Histologic examination shows definite hyperkeratosis with a typical keratohyaline layer and massive, nuclei-free horn platelets on the surface. Of special interest is the sharp, almost hair-like border between the area of leucohyperkeratosis and the normal epithelium. This sharp borderline is also characteristic of the carcinomatous layers, but here the borderline runs obliquely downwards, whereas in the areas of leucohyperkeratosis it is perpendicular. In the oblique carcinoma, demarcation lines are carcinoma cells in the basal layer and normal epithelium on the surface. The sharp straight but perpendicular borderline is characteristic of the hyperkeratosis. The oblique line of demarcation in carcinoma is the result of growth by assimilation in the basal layer; the shorter the time since the basal cells began their carcinomatous changes, the narrower the strip of carcinomatous cells which is regenerated by the basal cells. As a result, the thinnest layers of carcinomatous epithelium are to be found immediately over basal cells, which have undergone the most recent changes and vice versa. In this manner the oblique line is a sort of an indicator, pointing in the direction in which the carcinoma cells assimilate in the basal layer. In the hyperkeratotic leucoplakias the direction of the borderline is entirely different, it is just as sharp and linear, but always perpendicular to the basal layer; the line of demarcation between the two areas is at right angles to the surface. This finding can be explained by the

conclusion that these keratotic areas grow and extend toward, the periphery either very slowly or maybe not at all. In any case, with a sharp demarcation the straight course of the borderline is a regular and constant characteristic of this type of parakeratosis.

Close analysis of the changes involved in such an area of para- or hyperkeratosis will show the following:

1. The basal layer is the least affected. The cells are spindle shaped, have large nuclei and little protoplasm.

2. The prickle-cell layer is increased in thickness at the expense of the superficial layers. The thickness of the entire epithelium thus sometimes remains unchanged. In the normal epithelium the prickle-cells contain less protoplasm and show traces of glycogen as they approach the surface. In parakeratosis the prickle cells become more dense, homogeneous, and flat as they approach the surface. There is a gradual change so that the most superficial layers are composed of flat, homogeneous, dark-staining leaflets with almost black, shrunken nuclei in the center. Hyperkeratosis is merely a more advanced form of this differentiation. A keratohyalin layer is formed with a nuclei-free layer of hornified cells on the surface.

In leucokeratosis the stroma and papillary bodies show no changes whatsoever; signs of inflammatory infiltration are usually absent. In carcinomatous layers however, there is inflammatory infiltration of the stroma underlying the epithelium affected.

I had the opportunity to make clinical and histologic observations of a number of cases of leucokeratosis. Some of the cases have been followed for over five years. This group includes only cases which showed no evidence of syphilis, prolapse, or descensus. Search for signs or symptoms common to all the cases yielded very little. Thorough physical examinations, blood chemistry (cholesterol, etc.) and blood morphology also revealed nothing. As long as we cannot find characteristic general symptoms common to most of these cases we will have to regard this group of leucokeratosis as a result of local stimuli. These stimuli may be physiologic or pathologic.

Among a great number of leucoplakias, I found only nine cases of true leucohyperkeratosis without syphilis or prolapse. The ages of these patients ranged between twenty and forty; not one was postclimacteric. In older women, areas of leucokeratosis were always found to be associated with descensus or prolapse. Apparently the vaginal and portio epithelium loses so much of its reactive properties at menopause that a circumscribed local protoplasia can no longer occur. In none of these nine cases was there any evidence of beginning carcinoma. These areas of leucoplakia were unstable. Sketches made at each examination showed these bright spots with blurred borders changing their shades, outline, and location on the portio. Repeated histologic examinations showed that the parakeratosis never reached a high degree. The epithelium formed a superficial, thin, incompletely hornified layer with numerous nuclei remnants. Most of the cases described by Philipp and Schäfer probably belong to this group.

The transition to the rather small group of areas of leucohyperkeratosis is represented by a few cases. Here the areas of leucoplakia have sharply defined borders, a brighter appearance and are more stable from the point of view of development and localization. Colposcopic examination reveals, sometimes even without the use of iodine, small, bright, sharply defined spots, frequently slightly elevated. The following is a typical case:

CASE 3.—H. S., aged eighteen years. First menstruation at fourteen, irregular, every four to eight weeks, lasting eight or ten days. Patient complained of a four-month amenorrhea period and a loss of weight. Gynecologic findings: Normal sized uterus, anteverted, flexed, hard, movable; adnexa and parametria negative. On the anterior portio lip there was a small, oval-shaped, sharply defined, somewhat elevated area of leucoplakia. Histologically it consisted of thickened parakeratotic epithelium with beginning hyperkeratosis. In other words, it was a transition of leucoparakeratosis to leucohyperkeratosis (Fig. 2). Medical examination and

Fig. 2.—Case 3. Horizontal section, parakeratosis with a small patch of complete hornification; note the superficial layer without nuclei to the right of the midline. (×140.)

Wassermann were negative, blood chemistry was normal. Thorough follow-up for one year showed no changes in the clinical or histologic picture. After partial, and even complete removal of the area of leucoparakeratosis with a curette, it regenerated, identical in size and shape. This restitution, even after thorough removal, suggested that the cause for the prosoplastic changes of the epithelium was in the underlying stroma rather than in the epithelium itself.

Over a period of many years I found nine cases of genuine, spontaneous areas of leucohyperkeratosis. In four of these the uteri were extirpated for various other reasons so that we had the opportunity to study serial sections. Long clinical observations of these four cases were therefore impossible.

The following are typical cases of leucohyperkeratosis:

CASE 4.—M. N., aged forty-three years. Menstruation began at twelve, every four weeks, two or three days' duration, with cramps. Last menstrual

period five weeks ago. Patient never had sexual intercourse. She complained of a yellow fluor of one month's duration; this became bloody tinged lately. Gynecologic findings: One finger admitted with ease; uterus was of normal size, somewhat retroflexed, hard, and movable; parametria and adnexa negative; small cervical polyp protruding through the os; white vaginal discharge. During a curettage the uterus was perforated and was therefore extirpated. Histologic examination of the portio showed extensive areas of parakeratosis developing from three-layered epithelium with intermediate cornification. In one area the parakeratosis was replaced by an area of keratosis with a keratohyalin layer. In the basal layer there were edematous cells, the type which was sometimes found near beginning carcinomas* (Figs. 3 and 4).

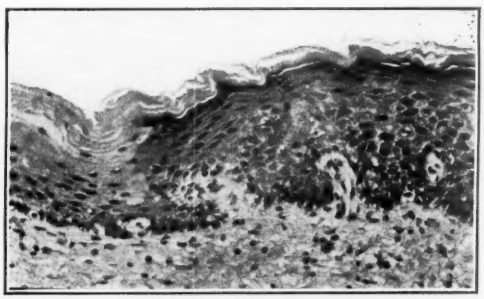

Fig. 3.—Case 4. Area of parakeratosis, left, and hyperkeratosis, right; note the sudden change and the vertical borderline between the two.

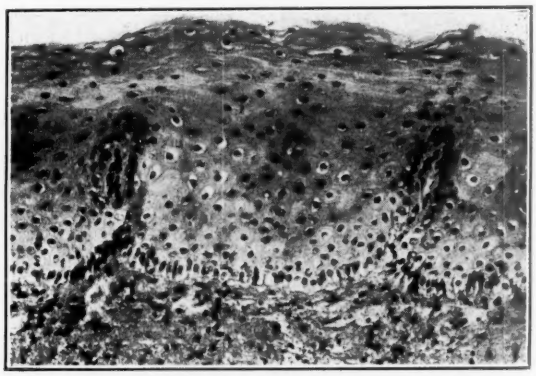

Fig. 4.—Case 4. Portio epithelium with parakeratosis; the cells of the basal layer are very edematous. (×5.)

This case deserves special attention because of the patient's virginity and negative Wassermann; external causes cannot explain the prosoplastic hornification. The cervical polyp was also no determining factor because cervical polyps are very seldom found together with hornified portio epithelium. It is probably a local process, comparable to the congenital hyperkeratosis of the skin.†

*Schiller: Arch. f. Gynäk., **130**: 263, 1927, Fig. 18.

†I have examined three surgical specimens of uteri which were extirpated from virgins; one was from a forty-seven-year-old patient, extirpated because of adenomyoma; one was a corpus carcinoma from a fifty-two-year-old woman; and one was a fibroid from a forty-six-year-old woman. In none of the three cases was the portio epithelium of the ideal type, there were patches of parakeratosis, narrowing of the epithelium due to inflammation, etc. The most marked changes were in the case of adenomyoma where the epithelium formed irregular, pointed, and plump plugs. (Fig. 19A in Wien. med. Wchnschr. **36**: 1172, 1931.)

CASE 5.—H. P., aged twenty-four years. Menstruation began at twelve years, every four weeks, lasting four or five days, regular until two months ago, para o, gravida o. Irregular vaginal bleeding and low back pain for past two months. Gynecologic findings: Normal sized uterus, hard, movable, anteverted, flexed; left ovarian cyst about the size of a walnut. On the anterior portio lip there was a small, bright, somewhat elevated area of leucoplakia with a dull surface and sharp borders. No other physical findings; Wassermann negative.

Histologic findings: A typical area of hyperkeratosis of the pavement epithelium with a well-developed keratohyalin layer and a wide, homogeneous nuclei-free horn

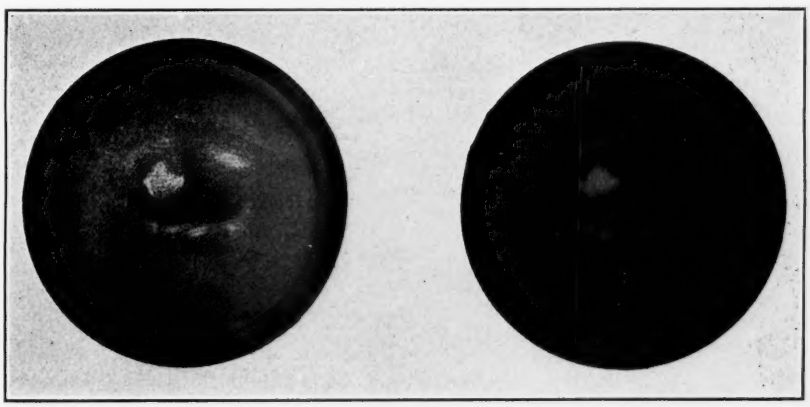

Fig. 5.—Case 5. (a) Cervix, a sharply defined bright leucoplakia to the right of the anterior lip. (b) Iodine application sets the lesion off as a white, sharply demarcated leucoplakia.

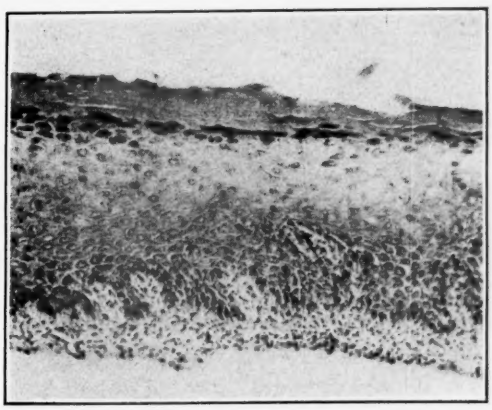

Fig. 6.—Case 5. Leucohyperkeratosis with cornified epithelium; well developed keratohyalin layer with a fairly thick, nuclei-free horn layer. (×140.)

layer. Close follow-up for over one year and a half showed neither gross nor microscopic changes. Repeated curettage of the lesion did not alter the picture (Figs. 5 and 6).

CASE 6.—G. G., aged thirty-three years. First menstruation at eighteen, irregular, every three or four weeks, lasting eight to twelve days. Sharp pain in the sacral region for some time; leucorrhea. Vaginal examination revealed no pathology. On the anterior lip there was an extensive, sharply defined, bright area which was histologically a typical leucohyperkeratosis.

CASE 7.—A. W., aged forty years. Menstruation began at thirteen, every four weeks, lasting three days. Nulliparous, six abortions. Wassermann negative. Patient complained of diffuse low abdominal pain and fluor of several weeks' duration. Vaginal examination negative. Iodine application and colposcopic examination revealed a more or less well-defined area of leucoplakia next to an erosion. Histologically it consisted of thickened, parakeratotic epithelium which occasionally

Fig. 7.—Case 9. Hyperkeratotic epithelium, distally from the external os, covering cystic cervical glands. (×50.)

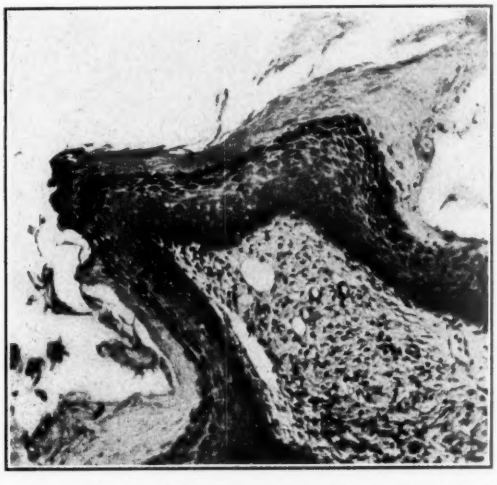

Fig. 8.—Case 9. Hyperkeratotic epithelium covering the space between two depressions that correspond to cervical glands. (×140.)

plugs erosion glands by means of plump cones. Some areas showed beginning cornification. Follow-up for several months showed slight regression of the areas of leucoplakia. The last examination showed areas of slight parakeratosis.

CASE 8.—M. W., aged forty-nine years. Menstruation began at sixteen, irregular, every four to eight weeks, lasting three or four days. Multipara, one abortion. Sacral pain of eight days' duration. Gynecologic findings: Uterus was plump, anteverted, markedly retroflexed; adnexa negative. Colposcopic examination showed

extensive areas of leucoplakia on both portio lips. Wassermann negative. Repeated examinations over one year showed no important clinical or microscopic changes. Occasionally the hyperkeratosis regressed to a parakeratosis.

CASE 9.—M. N., aged thirty-two years. Normal menstrual cycle since the age of eleven, gravida o. Wassermann negative. Patient complained of vaginal discharge. Vaginal examination negative. On the posterior surface of the portio there was a white, sharply defined, wartlike lesion. Histologic examination revealed an advanced, true cornification area. In view of the extensive lesion and advanced pathology, the cervix was amputated. Examination of the amputated cervix showed an extensive, healing erosion, partly glandular and partly cystic. Most of the surface epithelium over the erosion was markedly cornified. The keratohyalin layer and the desquamating horn layer were fairly thick (Figs. 7, 8, and 9).

Notwithstanding long follow-up studies of numerous cases, I have never as yet found areas of leucoparakeratosis or leucohyperkeratosis developing into carcinoma. In 1928 I published the case of a forty-

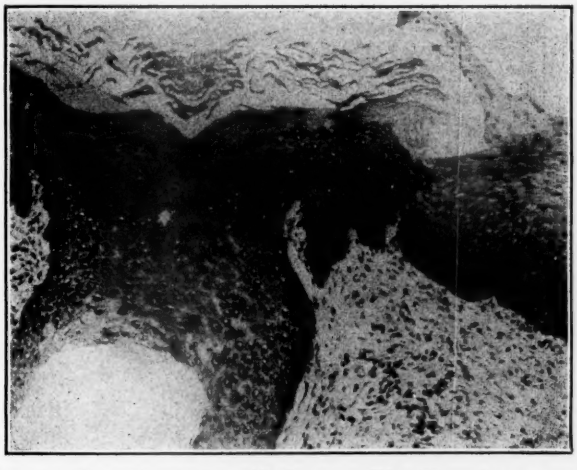

Fig. 9.—Case 9. Hyperkeratotic epithelium proliferating along a cervical gland, on the right a sharp vertical line of demarcation against the normal epithelium. (×140.)

four-year-old woman whose uterus was removed because of fibroids (Arch. f. Gynäk. 133: 253, 1928). I found an area of marked parakeratosis of the cervix which goes over in a carcinomatous layer. One exceptional case, however, is not sufficient to prove the relationship between areas of parakeratosis and carcinoma. Among many thousand cases I examined I found only one more case of a similar type:

CASE 10.—St. P., aged thirty-eight years. Menstruation began at twelve, normal cycle, regular until a short time ago. Para ii, one abortion followed by curetting. Patient complained of severe low back pains and dizzy spells. Examination revealed a fibroid uterus which was extirpated in the usual manner. The ovaries were found to have various-sized cysts.

Microscopic findings: The portio epithelium extended into the cervical canal. On the posterior lip, the epithelium, which contains islands of parakeratosis, very abruptly passed into a carcinomatous layer. On the anterior lip, the normal epithe-

lium very abruptly, under a sharp line of demarcation, changed into parakeratotic epithelium. In this parakeratotic zone, there was a small patch of normal epithelium sharply demarcated on both sides; it apparently corresponded to an *interlocking* between the normal and parakeratotic epithelium. About 6 mm. above the external os in the cervical canal, the parakeratotic epithelium directly passed into a carcinomatous layer (''Belag'').

In this case the carcinomatous layer was covered, in certain areas, with a thin, easily recognizable layer of bright cylindrical cells. If one followed the cervical

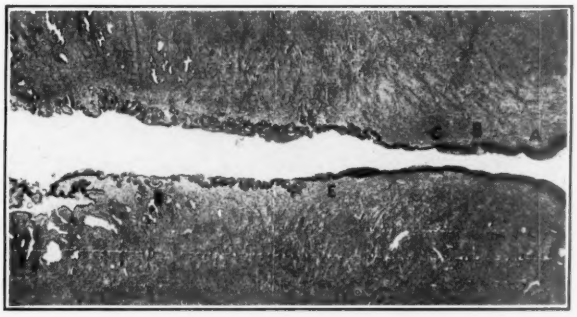

Fig. 10.—Case 10. Low power: Cervical canal, external os on the right. (A) The normal epithelium merging into parakeratotic epithelium. (B) A small plaque of normal epithelium within a parakeratotic zone. (C) Sharp, oblique borderline between normal epithelium and the carcinomatous layer. (D) Subcylindrical epithelium on the surface and around a cervical gland. (E) Carcinomatous layer and subcylindrical epithelium. (×6.)

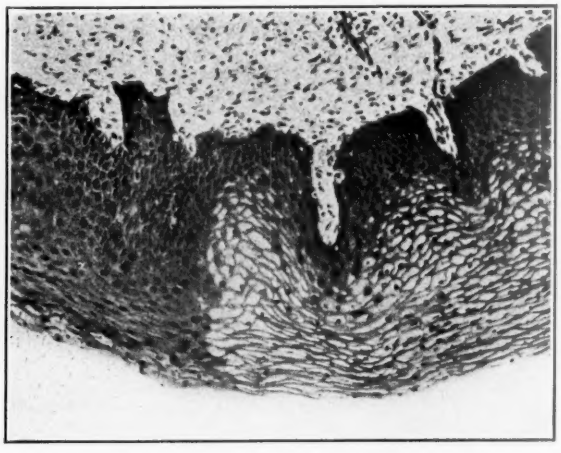

Fig. 11.—Case 10. (*A*, Fig. 10.) Normal epithelium right merging into parakeratotic epithelium, left. (×140.)

epithelium upward, one found partly ramified *(racemose)* glands and partly superficial cylindrical epithelium. As long as these cylindrical cells were an integral part of the superficial glands, or the superficial epithelium, they rested on one or more layers of solid cells. The deeper the cervical glands reached into the depth, toward the cervical wall, the less the number of subcylindrical cells encountered, and the less developed they were. The glands situated in the depth of the cervical wall had a normal appearance. Franqué investigated these so-called subcylindrical cells and Hinselmann described a typical case (Arch. f. Gynäk. 133: 64, 1928). Franqué does not regard these subcylindrical cells as the general origin of the glandular

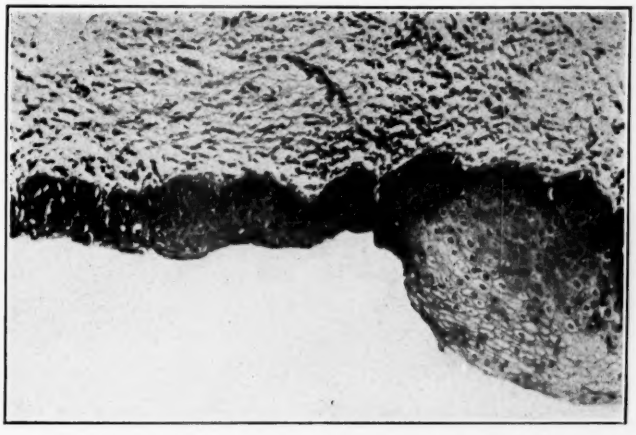

Fig. 12.—Case 10 (*C*, Fig. 10.) Oblique, sharp division line between the normal epithelium and the carcinomatous layer. (×140.)

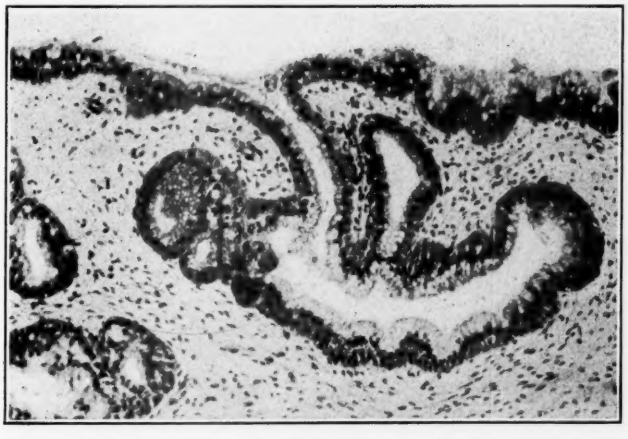

Fig. 13.—Case 10. (*D*, Fig. 10.) Subcylindrical epithelium covering the surface and surrounding a cervical gland.

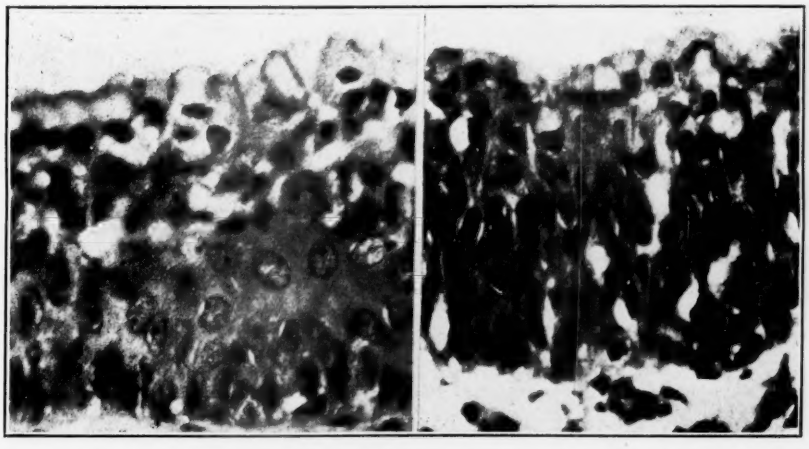

Fig. 14.—Case 10. (*E*, Fig. 10.) Showing carcinomatous layer functionating as subcylindrical epithelium. (×800.)

carcinomas of the cervix. In this particular case I have no doubt that the carcinoma developed from the subcylindrical cells. But it is a solid carcinoma and not an adenocarcinoma. Through this finding, that is, the development of the carcinoma from subcylindrical cells, this case loses an important point of analogy with the preceding case. Careful examination of serial sections did not reveal any subcylindrical cells in the cervical mucosa of the first case. In the first case the carcinomatous layer (''Beläge'') developed from the portio epithelium; in the second case from subcylindrical cells of cervical epithelium, which was adjoining a sharply demarcated parakeratotic zone of the portio. Even if we were permitted to offer these two cases as proof that superficial carcinomas can develop from parakeratotic epithelium, the evidence would be worthless because of the numerous beginning carcinomas which develop without even the slightest trace of advanced parakeratosis in the adjacent areas (Figs. 10, 11, 12, 13, and 14).

There is no causal relationship between para- or hyperkeratosis and carcinoma of the portio. From extensive material I could not find even one case of carcinoma that developed from a true keratosis.* Cases with prolapse are excluded in this study; at best they disprove any relationship between carcinoma and cornification. In other parts of the body, mouth, lips for example, cornification plays an important rôle in the etiology of carcinoma. This was definitely proved by Schwimmer, Brofeldt, Ullman, etc.†

The situation with the portio epithelium is as follows:

The carcinoma develops from epithelium which frequently shows slight prosoplastic changes, as exemplified by intermediate, incomplete three-layered cornification. At best this prosoplastic change is a prerequisite and not a cause for the growth of carcinoma. This three-layered intermediate cornification is frequently nonspecific and not associated with carcinoma. Advanced cornification, even the autonomous form does not give rise to carcinoma.

These areas of leucoplakia do not warrant radical treatment, such as amputation of the portio advocated by some authors as a prophylaxis against possible malignancy. We found that these areas of leucoplakia remain for years without undergoing any changes. Malignant degeneration after ten or twenty years cannot be excluded, but our observations as well as those of Philipp and Schäfer point against it. If the histologic diagnosis is definitely established a periodic examination is sufficient. Radical therapy is not justified. These areas of leucoplakia are to be grouped with the benign hyperkeratosis of the skin rather than with the leucoplakic areas of the mucosa of the mouth or larynx.

The carcinomatous layer of the portio grows by assimilation of adjacent normal cells without passing through any intermediate stages.

*In the cases published by Esser, Franqué, Geller, Labadie, Puccioni and so on as carcinomas after leucoplakias, the leucoplakias probably have been carcinomatous surface epithelium and neither keratosis nor para- nor hyperkeratosis.

†According to Brofeldt about 25 per cent of leucoplakias of the lips degenerate into carcinomas. This does not hold true for portio epithelium.

This view is supported by the manner in which the carcinomatous epithelium passes into normal epithelium, the change is abrupt, without any areas of transition.

In the cornified carcinomas of the skin, however, the onset is gradual, and there is an area of transition from the normal to the diseased tissue. Between the normal and carcinomatous epithelium there is an intermediate zone which is not yet carcinomatous, and yet no more normal. Here the assimilation of the adjacent epithelium is slow and gradual, and apparently the beginning carcinoma also develops in a similar manner. As a result of this slow assimilation some times histologic pictures turn up which make a clear-cut classification impossible. As Delbanco first described it, the epithelium is in a state of restlessness, that is, the epithelium is no longer normal because of polymorphous cells and nuclei, on the other hand it has not reached the fully developed carcinomatous character as yet.

In the portio carcinoma there are no such transitions in the intermediate zone or before the beginning of the carcinoma proper. A suspicious appearing area of the portio when examined histologically will turn out to be either a leucokeratosis or a carcinomatous layer (''Belag''). The difference between the two is so marked that there is never a question of differential diagnosis.

Proliferations of the epithelium, however, due to chronic inflammation do cause confusion sometimes. This is especially true when one finds excessive production of immature cells in the basal and prickle-cell layers. Under such circumstances the differential diagnosis between excessive proliferation and carcinomatous layer is not simple. Among several hundred biopsies I found five cases of this type. These were followed up very closely.

The following are two of this group:

CASE 11.—H. K., aged forty years. First menstrual period at sixteen, every four weeks, four to six days, regular until two years ago, multiparous. Patient thought she was pregnant because of eleven weeks of amenorrhea. Gynecologic findings: Normal-sized uterus, anteflexed, hard, freely movable, left parametrium shortened somewhat; white vaginal discharge. Iodine application brought out, on the posterior lip, several pale patches with blurred borders. Biopsy showed marked thickening through parakeratosis, the nuclei of the deeper layers were somewhat polymorphous. The basal layer contained numerous mitotic figures. The rapid proliferation caused deformity of cells and entire cell groups. The prickle-cell layer was mature, with well-developed strands of epithelium. The surface layer was composed of partly glycogen-containing cells and partly of areas of parakeratosis. The mitotic figures here did not point to malignancy because they were neither atypical nor irregular. An increased number of *regular* mitotic figures was of no importance, especially during pregnancy.* In view of the few polymorphous and atypical cells, ***excessive proliferation*** was diagnosed. Repeated biopsies for a period of eight years failed to show malignancy. Occasionally the proliferation and parakeratosis diminished in intensity (Figs. 15 and 16).

*Vasiliu determined, statistically, the numerical relationship between mitotic and resting nuclei, without utilizing his results to practical advantage.

CASE 12.—A. S., aged thirty-seven years. First menstruation at sixteen, every five weeks, lasting three or four days. Two normal deliveries, one followed by chills and fever. For the past month patient had had irregular vaginal bleeding which was aggravated by contact. Wassermann negative. Gynecologic finding: Gaping vulva, old scar tissue in perineum and anterior vaginal wall. There was an erosion on

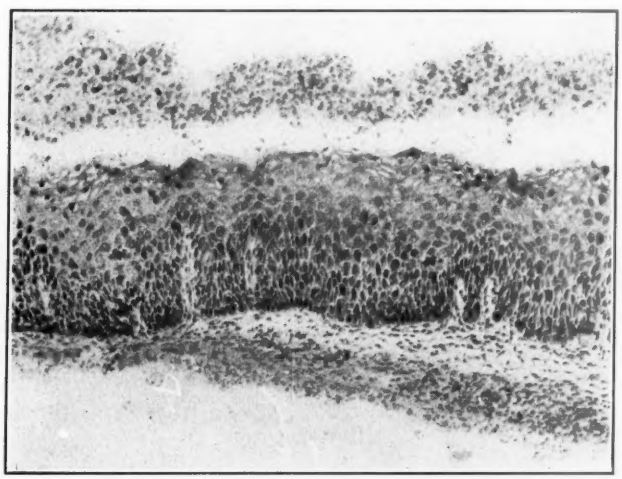

Fig. 15.—Case 11. Portio epithelium; the basal layer greatly increased in thickness at the expense of all other layers; frequent mitoses, the abnormal proliferation is causing crowding and deformation of the basal cells. (×140.)

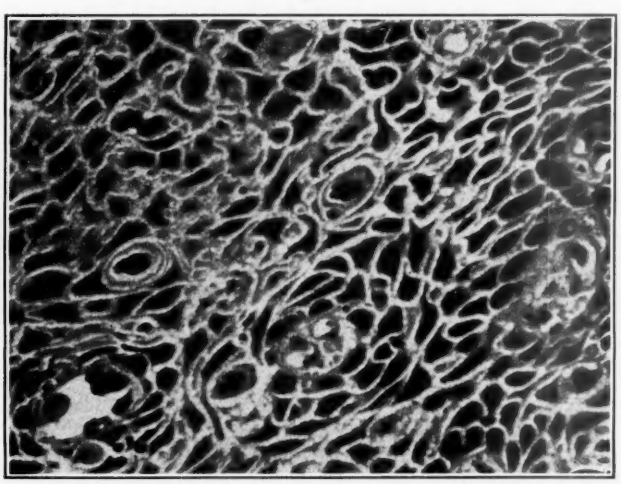

Fig. 16.—Case 11. Horizontal section through the basal layer; deformed nuclei, three typical mitoses, at the lower left a papilla and capillary cut transversely. (×700.)

the posterior lip. Iodine application left the erosion as a white patch. The posterior as well as the anterior lips had ragged craters with bleeding tissue at their bases. The edge of the erosion was composed of thickened epithelium, in a vascular network. The entire picture was that of an old, healing erosion. The squamous epithelium had a superficial, spongy glycogen-containing layer with areas of parakeratosis. The basal layer resembled the preceding case (Fig. 17); polymorphous or atypical

structures could not be found.* After four years the abnormal proliferation disappeared, but the parakeratosis increased somewhat in intensity. The gross appearance of the portio did not change.

These two cases are illustrations of abnormally rapid and excessive, but benign proliferation which may disappear in time. It is characterized by the accumulation of immature cells in the basal layer.

As in acanthosis the prickle-cell layer is increased in thickness in these cases, the basal layer is increased, which represents the *undifferentiated* zone or the *cambium* layer of epithelium. In these cases of pathologic proliferation, the mitoses are not confined to the basal layers only, they are also to be found in three or four cell layers overlying the basalis. This, however, is not due to an increased thickness of the basal layer which serves as an area of regeneration. As Thuringer pointed out, in

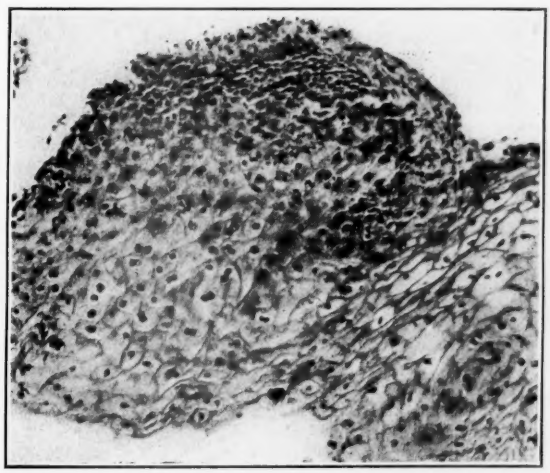

Fig. 17.—Case 12. Glycogen-containing, rapidly proliferating portio epithelium; most of the cells contain amitotic, double nuclei. (×140.)

the normal portio epithelium and in the squamous epithelium in general, mitosis in the prickle-cells immediately adjoining the basal layer is not uncommon. Nevertheless, in benign proliferation the epithelium above the basal layer reaches maturity, whereas in beginning carcinoma this is hardly true. The cause of such a benign proliferation is still unknown. We can offer an explanation only for a certain group of cases: During pregnancy there is a similar, but not such a marked change in the portio epithelium; there is a moderate increase in the thickness of the basal layer and in the number of mitotic figures. In these cases the proliferation is part of a general hypertrophy and hyperplasia of pregnancy. In cases without pregnancy endocrines may be responsible, thus drawing an analogy between this benign proliferation and the proliferation of the vaginal epithelium in rodents. This type of pro-

*In the prickle cell layer many cells show double nuclei.

liferation has nothing in common with malignant degeneration. As far as one may conclude from observations lasting for five to eight years, our cases of benign proliferation of the portio epithelium did not show the least tendency toward carcinomatous degeneration.

We still know very little about the precursors of portio carcinoma. Only in the negative sense can we draw several conclusions with a fair amount of certainty. According to Robert Meyer's, and my own investigations, neither erosions, nor inflammations form a basis for the development of carcinoma,* but even the leucokeratosis and the abnormal proliferation need not be regarded as precursors of portio carcinoma.

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Jewish Memorial Hospital

*The Cancer Research Committee of the Marie Curie Hospital, London, Report of 1936, p. 36. It is generally believed that cervical lacerations and chronic cervicitis are important factors in the etiology of cervical cancer. There seems to be little evidence to support this view, and in our investigations of degree 1 and 2 cases—usually the only cases suitable for such an investigation—lacerations have seldom been found or when present may not have shown any relation to the cancer.

THECA CELL TUMORS

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IN A RECENT publication, one of us (S. H. G.) called attention to a group of tumors of the ovary, which because of their definite histologic, chemical, and biologic characteristics were considered to be related histogenetically to the theca interna cells of the ovary or their precursors. While this group has some histologic and clinical resemblance to the granulosa cell tumors, the morphologic features are distinctly different. The theca cell tumors simulate in appearance a fibromatous neoplasm. Because of this resemblance, and stimulated by the finding of three additional cases, we were prompted to review those tumors of the ovary which had been reported previously in the laboratories of the Mount Sinai Hospital as fibromas, or fibro- or spindle cell sarcomas. We were able to add three additional instances which we believe can be classified as of theca cell origin.

Histologic studies reveal various gradations from the cellular, malignant theca cell tumors to the more fibromatous types. It is conceivable that the fibromas and spindle cell sarcomas described by Robert Meyer as possible end-results of granulosa cell growth, and also some other tumors associated with feminizing influences may in reality belong to the group of theca cell tumors.

The clinical and morphologic characteristics of six additional cases of theca cell tumors are reported. Attention is called to their histologic variations and differential features. In the light of this investigation it is hoped that a sharper delineation of the theca cell tumors will be possible and their recognition and separation from the group of fibromatous ovarian tumors facilitated.

CASE 1.—Mrs. B. G. (P-3737, Courtesy of Dr. A. A. Berg) was admitted to the private pavilion of the Mount Sinai Hospital in December, 1929, because of left lower abdominal pain of several months' duration. She was fifty-five years of age, and aside from the fact that there had been no bleeding since her menopause, the history did not include any reference to somatic variations which might be interpreted as dependent upon abnormal hormonal changes.

Examination revealed the presence of a cystic mass in the region of the left adnexa. At operation a left ovarian tumor was removed. No notation was made at that time concerning the size of the uterus, nor was endometrial tissue obtained to determine a possible estrogenic effect of the ovarian neoplasm.

Pathologic Anatomy

Gross.—The specimen was approximately the size of a grapefruit, and cystic (Fig. 1). It replaced the ovary entirely and measured 15 by 12 by 11 cm. An intact

capsule encased the yellow tumor. The wall varied in thickness from 2.5 cm. at one pole, to paper thinness at the other. In the latter region there was evidence of hemorrhage into the wall. On *section* through the tumor it was found to be firm, fibrous and yellow. Grossly the tumor appeared to be an ovarian fibroma with cystic degeneration. The distinct yellow hue, however, and the rather cellular appearance suggested the possibility of a theca cell neoplasm.

Fig. 1.—Case 1. Cystic ovarian tumor with fibrous, yellow wall. Note thickness of wall at the right pole.

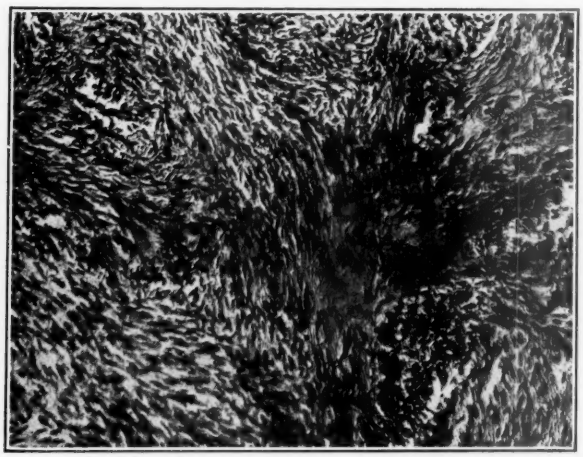

Fig. 2.—Case 1. Interlacing bundles of fusiform and epithelioid cells merging towards a hyalinized plaque.

Microscopic.—The histologic picture showed several characteristic features. The tumor was composed of interweaving bundles of closely packed cells cut in longitudinal and cross-section. Some areas were characterized by cells of a fusiform or spindle shape, but the more prominent type cell appeared polygonal or epithelioid, with a vesicular nucleus and a vacuolated cytoplasm. A delicate fibrillar arrangement of connective tissue separated the individual cells. Small hyaline plaques were numerous, and stood out prominently in the midst of the cellular bundles (Fig. 2).

From them fine fibers extended in a radial or tangential fashion into and about the surrounding epithelioid cells. The lipoid stain demonstrated many minute sudanophilic droplets scattered within the cellular areas which were doubly refractile on polaroscopic study.

CASE 2.—The ovarian tumor described below was presented to us through the courtesy of Dr. William Anopol. Many of the clinical data were not obtainable, but the gross microscopic features were typical of a theca cell tumor. The patient was

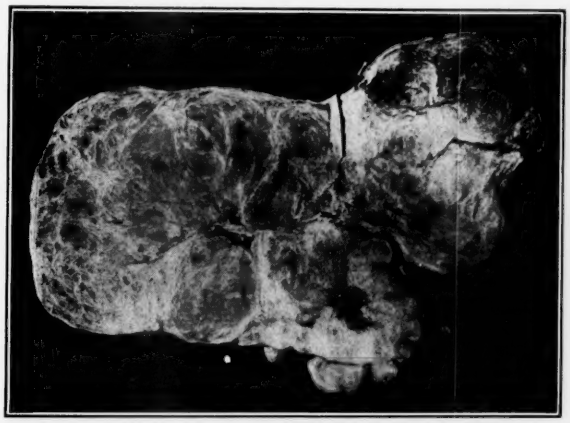

Fig. 3.—Case 2. Yellow, lobulated tumor with white, fibrous septa.

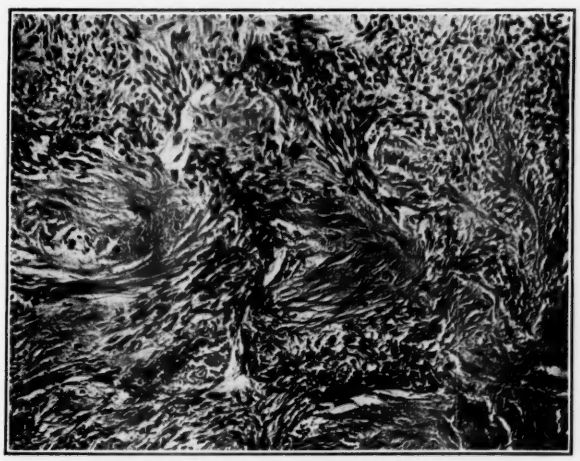

Fig. 4.—Case 2. Typical hyaline plaques with fibrous extensions into epithelioid cell groups.

a forty-six-year-old woman whose menses had always been irregular. Following amenorrhea of three months a period had occurred six weeks previous to admission. *Bleeding recurred and continued for two weeks before operation.*

Pathologic Anatomy

Gross.—The resected specimen consisted of a firm, nodular, solid ovarian tumor which measured 17 by 9 by 8 cm. (Fig. 3). Its surface was studded with numerous bosses of varying size. The ivory white capsule was complete throughout, but here

and there, the yellow color of the underlying tumor tissue could be seen. The neoplasm cut with a grating sound because of the abundance of fibrous tissue present. Cross-section showed a lobular structure. Thick strands of white fibrous tissue ramified throughout the tumor, separating numerous small and larger lobules of yellow cellular tissue. At one pole, there was an area of old hemorrhage.

Microscopic.—The characteristic features of irregular cellular strands separated by crescents or islands of acellular or hyalinized tissue was most conspicuous (Fig. 4). In the former areas the cells were closely packed and epithelioid in appearance. The nuclei were oval with blunted ends, or plump and spindle shaped, and rather vesicular. The azo-carmine stain emphasized the thin connective tissue fibrils which merged into the thicker collagenous fibers of the surrounding plaques. The yellow color was due to the large quantity of fat droplets within the cytoplasm of the cellular portion. A moderate quantity of these lipoid particles were doubly refractile.

CASE 3.—(48219) G. F., sixteen years of age, was admitted to the gynecologic service in July, 1933. Her complaints included a primary amenorrhea and four months of lower abdominal discomfort. In addition, she had noted a tendency to hypertrichosis and a coarser quality to her voice over a period of four years. The general stature was feminine, but somewhat infantile, with a normally feminine shoulder-hip ratio. Her height was four feet, eight inches. The breasts were well developed for her age. Her voice seemed harsh. The fingers were short and thin and the joints showed excessive relaxation. There was some hirsuties, especially of the abdomen and the lower extremities. A slight mustache and long soft hair at the sides of the face were evident. The escutcheon was of the male type, and the clitoris was enlarged to 3 times the normal size, with definite overdevelopment of the prepuce. The hymen admitted one finger, and the vagina was somewhat contracted. The cervix appeared normal in size, sinistroverted and retrocessed. Posteriorly in the culdesac and to the right a hard irregular, freely movable mass the size of a small melon could be felt. At operation a bilateral salpingo-oophorectomy was performed.

Pathologic Anatomy

Gross.—The right ovary was replaced by a solid, firm tumor the size of an orange and measured 8 by 5 by 5.5 cm. (Fig. 5). The contour was oval and the surface smooth with an occasional irregular elevation. A complete capsule surrounded the gray yellow neoplasm. On section many small particles of calcified tissue were encountered by the knife. The tumor was divided by white fibrous septa into round or irregular yellow lobules. The individual lobulations presented a whorl-like appearance. The *left ovary* was enlarged to the size of a walnut and was similar in appearance to that of the right.

Microscopic.—The first microscopic section examined showed for the most part a typically fibromatous appearance, with wide strands of thick collagenous fibers, distributed in an irregular fashion. Further study, however, revealed many areas of different structure. These were moderately cellular and included broad bundles of basophilic epithelioid cells surrounded and encroached upon by partially hyalinized connective tissue strands. Many small plaques of calcification were present in the more fibrous portions. Fat stains and polaroscopic study showed the typical distribution of intracellular, doubly refractile lipoid particles.

CASE 4.—(P-5239, Courtesy of Dr. A. A. Berg) B. P., a fifty-seven-year-old woman, was admitted in January, 1932, complaining of severe uterine bleeding, several years after the menopause. A large mass the size of a grapefruit could be felt in the

region of the left adnexa in addition to multiple fibromyomas of the uterus. At operation a supravaginal hysterectomy and left salpingo-oophorectomy and appendectomy were performed.

Pathologic Anatomy

Gross.—The resected uterus was enlarged to the size of a ten-weeks' gravidity by the presence of small intramural fibroids. It measured 10 by 7 by 5 cm. The

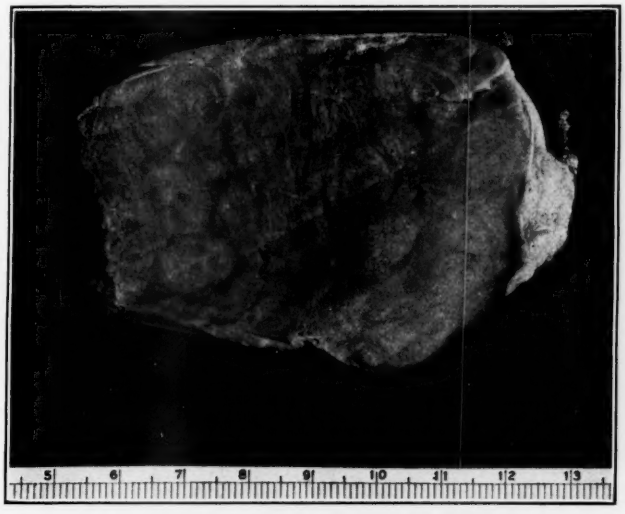

Fig. 5.—Case 3. Solid, yellow tumor lobules separated by white connective tissue septa.

Fig. 6.—Case 4. Solid, encapsulated tumor with large yellow areas.

endometrium appeared hyperplastic and contained a small polyp in the region of the right horn. The left ovary was replaced by a solid ovarian tumor the size of a large orange, 12 by 8 by 8 cm. (Fig. 6). The surface was studded with numerous, small, firm nodules varying in color from ivory to yellow. The cut surface presented a lobulated structure. The strands of gray, fibrous connective tissue completely encapsulated the tumor, extending into it and separating the cellular yellow tan, bulging lobules.

Microscopic.—A marked cellularity was apparent on microscopic section, the tumor being composed of densely packed, plump, elongated spindle cells without any regularity of arrangement (Fig. 7). The nuclei of these cells were round or oval, large, pale and vesicular. Areas were to be found also in which the cell type was narrower and more fusiform, with slender, darker staining nuclei. Bundles of such cells especially when cut on cross-section suggested the appearance of smooth muscle tissue. At times at the periphery of some of the smaller lobules, very fine bands of

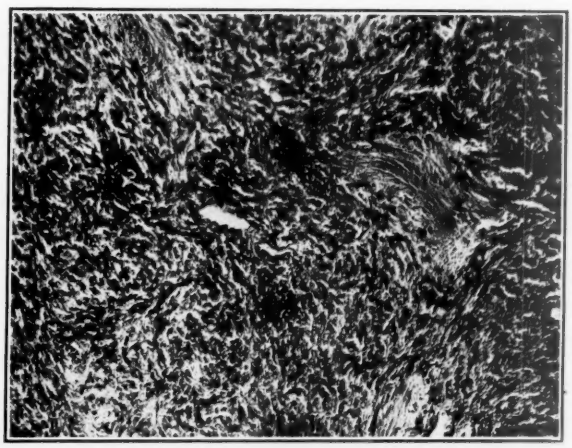

Fig. 7.—Case 4. Closely packed epithelioid cell bundles about a hyaline plaque.

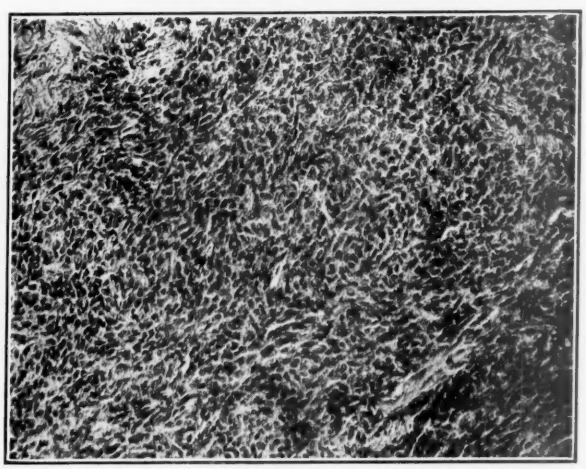

Fig. 8.—Case 4. Markedly cellular tissue suggesting possible luteinization.

darkly staining, somewhat irregular and atypical cells could be seen. The tumor on the whole was vascular, containing both thin-walled capillaries and larger-sized vessels. There was some necrosis and hemorrhage present but not to a conspicuous degree. Hyalinization was not marked. The predominant type of cell was definitely epithelioid in character and closely packed, suggesting the structure of theca cells. Mallory stain demonstrated the distribution of fine fibrillar connective tissue between the cells. A moderate amount of cell atypism with nuclear variations and rare mitotic figures was noted. Though some of the cells could possibly be interpreted as re-

sembling granulosa cells (Fig. 8), no single area was found that in our opinion could be classified as a granulosa cell tumor tissue, not even of the atypical (spindle cell) variety. When stained with Sudan III an abundance of fine globules of fat was present. These included cholesterol or cholesterol esters as shown by their doubly refractile nature under polarized light. The uterine endometrium showed a hyperplastic appearance (Fig. 9).

CASE 5.—(P-10051, Courtesy of Dr. A. A. Berg, January, 1936). The patient was a forty-nine-year-old French cook who had never married. The menarche had begun at twelve, with regularly occurring periods every twenty-eight to twenty-nine days, lasting four to five days. The flow was moderately profuse. At the age of forty-six her menses began to decrease and become irregular. The menopause was complete one year later without further recurrence of bleeding. Eight months previously she had been hospitalized at another institution for eight weeks, supposedly for a bronchopneumonia involving the right lower lobe. The present complaints were of two and one-half months' duration and included swelling of the abdomen, a gain

Fig. 9.—Case 4. Hyperplastic endometrium, postmenopausal.

of twenty-two pounds in weight, constipation, occasional nausea and vomiting, anorexia and polydipsia. The temperature during the two days before operation ranged from 100.6° to 102° F. and the pulse from 112 to 120.

At operation two quarts of serosanguineous ascitic fluid were removed. A large irregular right ovarian tumor was found, with numerous adhesions to small and large bowel. Many small metastatic nodules were seen scattered throughout the peritoneal cavity especially in the broad ligament and posterior culdesac. The adhesions were separated and the tumor removed.

Pathologic Anatomy

Gross.—The neoplasm was a large, firm, irregular, oval shaped, yellow gray ovarian tumor, weighing 2375 gm. and measuring 21 by 20 by 14 cm. (Fig. 10). The surface was nodular. It was rather well encapsulated except for several small areas where the tumor tissue had perforated the capsule and appeared as small granular excrescences on the surface. Fibrous adhesions were present. On section the tumor could be divided roughly into two portions. One was composed of rather solid, medullary, cellular, grayish white tissue in which small, yellow areas were interspersed.

Here and there one could see small cystic zones and occasional hemorrhagic spots. The other portion was made up basically of hemorrhagic, degenerated, gray brown tissue containing large cavities lined by shaggy necrotic material. The lining of one small cavity was yellow and granular.

Microscopic.—The tumor appeared markedly cellular, with large areas of degeneration and hemorrhagic infiltration. Several portions looked sarcomatous, pre-

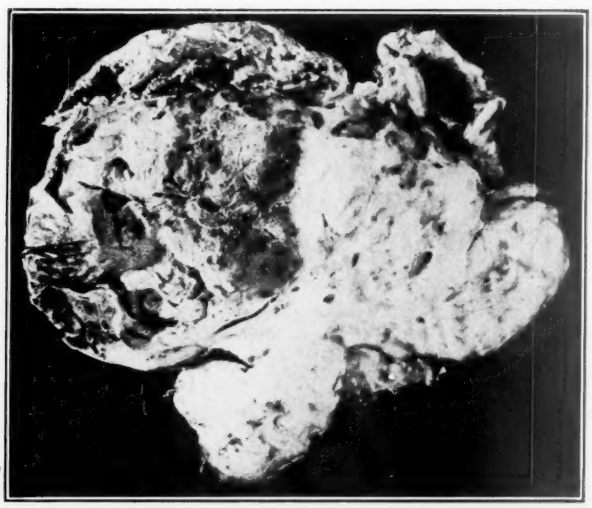

Fig. 10.—Case 5. Solid, degenerated, cellular tumor with perforated capsule. (Malignant.)

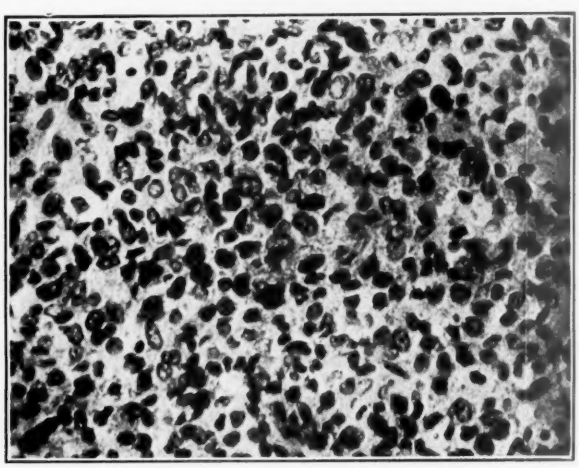

Fig. 11.—Case 5. Large, atypical, malignant, cellular areas.

senting conspicuous alterations in the cell and nuclear structure, mitoses, variability in staining reaction, and penetration through the surrounding capsule. The cells in these areas were not fusiform in shape, but rather epithelioid or round in appearance (Fig. 11). In the more benign, cellular portions irregular strands of plump, spindle cells interlaced in a haphazard fashion. Here numerous islands of polygonal cells with central nuclei were found. Fine fibrils extended between the individual cells and merged into the thicker connective tissue bundles which traversed

the entire tumor. Small hyaline plaques were scattered throughout (Fig. 12). In the substance of the tumor small glandular areas lined by high cuboidal epithelium could be seen which had a benign appearance and probably represented inclusion cysts from the peritoneal surface. This seemed especially evident in those sections showing nodular elevations of the tumor in close apposition. Frozen sections stained with Sudan III revealed numerous, fine fat droplets situated for the most part intracellularly and in cells which did not show any evidence of degeneration. Polaroscopic study showed the doubly refractile fat to be confined to the cellular areas and absent in the acellular or degenerated portions.

CASE 6.—(Courtesy of Dr. H. M. Rabinowitz and Dr. M. Jacobi, Beth El Hospital, Brooklyn, N. Y.) B. S., aged fifty-nine, was admitted to the Beth El Hospital in October, 1936, for postmenopausal bleeding. She had borne two living children and had experienced four spontaneous miscarriages and one ectopic pregnancy. On the latter account a left salpingo-oophorectomy had been performed twenty-five years before. Following her menopause at the age of fifty, the patient was well for six years. During the past three years, extending to the time of admission there had

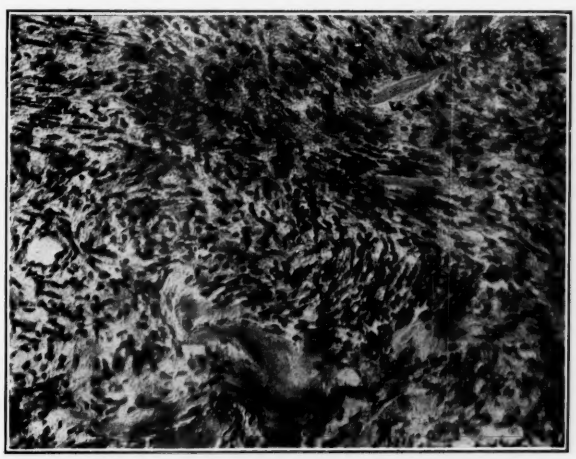

Fig. 12.—Case 5. Cellular but more regular spindle cell areas with hyaline plaque.

been intermittent vaginal bleeding of varying intensity, separated by periods of amenorrhea. Physical examination revealed the presence of a mild hypertension and a moderate secondary anemia. On pelvic examination the cervix was firm and lacerated, with active bleeding from its canal. The uterus was globular and enlarged to the size of a seven to eight-weeks' gravidity. In the right fornix, a hard, freely movable mass the size of a large walnut could be felt. A preliminary curettage showed polypoid hyperplastic endometrium. The presence of bleeding after the menopause, hyperplastic endometrium and a firm ovarian tumor pointed strongly to the diagnosis of ovarian, feminizing neoplasm which could be either a granulosa or theca cell tumor. A supravaginal hysterectomy and right salpingo-oophorectomy was therefore performed.

The resected uterus was enlarged approximately to the size of a seven-weeks' gravidity. It contained a few small, intramural fibroids varying from a pea to an almond in size. The serosa was smooth and the myometrium thickened to 3 cm. On section it presented a pink gray surface which was marked by the presence of numerous small areas containing old blood and an irregular arrangement of interlacing strands of fibromyomatous tissue. The gross picture was typical of adenomyosis.

The endometrial cavity measured 6.5 by 3 cm. Though much of the endometrium had been removed by a previous curettage, portions still showed a hyperplastic appearance. The fallopian tube was normal in size and configuration, although somewhat atrophic. The right ovary was replaced by a solid tumor, oval in shape and approximately the size of a small lemon. It measured 6 by 4 by 2.5 cm. The surface was irregular and nodular and its thin capsule intact. Its color was a mottled yellow white (Fig. 13). On section one portion seemed densely white and fibrous. Another was divided into lobules separated by white strands of irregular width. Some of the lobules presented a cellular, yellow tan appearance. Others were lighter in color and more fibrous, as though a greater concentration of thin

Fig. 13.—Case 6. Theca cell tumor (actual size).

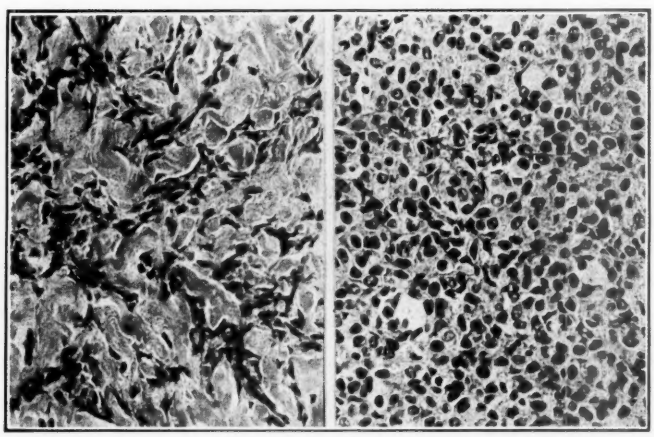

Fig. 14.—Case 6. Variations in the degree of cellularity within the same tumor.

fibers separated the cellular elements. One of the larger lobules measuring 1.75 by 1.25 cm. was cystic, the lining being covered by an irregular shaggy yellow tissue.

Histologic study proved unusually interesting because this ovarian neoplasm was illustrative of many variations encountered in different theca cell tumors (Fig. 14). Uniformity is not a constant feature of this type of tumor, the final picture depending upon the degree of cellularity, the tendency toward fibromatous and hyaline changes, degeneration and cyst formation. The areas seen as white and firm were found to be fibrous, but included numerous, markedly cellular strands. In many of these, among densely packed, oval-shaped cells, hyaline cords were conspicuous. The yellow lobules which stood out so prominently on gross examination were recognizable as conglomerations of large, epithelioid and oval cells. In some of them one could trace a gradual transition from the periphery inward; from the spindle to

epithelioid or oval cells, and finally to those which might be interpreted as theca lutein in appearance. The cells were for the most part oval or epithelioid, with vesicular nuclei and distinct nucleoli. The cytoplasm appeared foamy. Scattered, single, hyperchromatic nuclei were occasionally seen, and rarely, mitotic figures. Areas of degeneration and edema were not infrequent. The lipoid stain corroborated the expected, typical distribution of fine, intracellular, sudanophilic droplets, often not visualized except under high magnification. The uterine myometrium showed a marked adenomyosis. The endometrium was distinctly hyperplastic.

DISCUSSION

An analysis of the six cases described above together with those published in 1935 (5 cases) indicates that a definite classification of theca cell tumors is possible. The tumors may vary from moderately fibrous types to those showing marked cellularity or even malignant characteristics. To date, of the 22 cases reported in the literature only two were malignant; one described by Loeffler and Priesel and the other included in this paper. Genetically, the theca and granulosa cells have a common origin. In the course of neoplastic development either a pure theca or granulosa cell tumor may result. Because of their similar genesis, it is not inconceivable that a tumor containing both theca and granulosa cell tissue may occur.

The presence and distribution of fat within the theca cell tumors is of particular interest. It occurs far more extensively within the cellular islands than in the connective tissue framework. Polaroscopic examination reveals the lipoid to be doubly refractile, indicating the presence of cholesterol or cholesterol esters. Examination of fibromas, spindle cell fibrosarcomas and many other ovarian tumors failed to show this characteristic fat distribution, but the phenomenon was demonstrable in a granulosa cell tumor and to some extent in an arrhenoblastoma. Thus, of all the ovarian tumors studied only those possessing masculinizing or feminizing tendencies had this characteristic in common. We know, moreover, that the chemical structure of both the male and female sex hormone is closely related to cholesterol. It would seem therefore that within ovarian neoplasms a definite association exists between the presence of doubly refractile fat (cholesterol and cholesterol esters) and the tendency to induce sex changes. It is interesting to note that the dysgerminoma, a tumor which has no incretory function and does not affect the individual either in a masculine or feminine direction, fails to show intracellular fat.

Outside the ovary such lipoid storage may be seen in histiocytomas or xanthic fibromas of the skin, pseudoxanthomas and xanthomatoses or xanthic lipoidoses. These, however, are apparently manifestations of a reticulo-endothelial system response to a destructive or irritant process or to a disturbance in lipoid metabolism. As is well known some of these cases are associated with hypercholesterin-

emia. In one case of theca cell tumor recently published (S. H. G.) no disturbance of cholesterol metabolism was found. The question arose whether or not the cholesterol esters present in the theca cells were evidence of a histocytic function and whether theca cells possessed histocytic properties. Small quantities of lithium carmine (3 to 5 c.c.) were injected into the ear veins of virgin and parous rabbits at two-day intervals for a period of two weeks. The granulosa and theca cells of the well-preserved follicles remained free of carmine particles, as did the granulosa lutein and theca lutein cells. The carmine, however, was evident in large amounts within the plump, fat containing cells of the degenerating follicles or corpora lutea, and in an occasional cell within the ovarian parenchyma. The carmine containing cells were interpreted not as theca cells but as histocytes called forth as a response to the degenerative process affecting the follicle or corpus luteum. Neither the normal theca or granulosa cells apparently acted as histocytes.

We feel that we have been able to identify as a separate entity, a group of tumors whose clinical course includes not only those symptoms associated with any pelvic neoplasm, but also physiologic changes which are quite characteristic. These tumors most commonly occur in women past the menopause, though they have occasionally been found before the climacterium. Atypical bleeding is the most prominent symptom in the postmenopause cases, while metrorrhagia followed by a period of amenorrhea is frequently complained of in the younger women. There is often slight enlargement of the breasts and of the uterus. The endometrium presents a hyperplastic picture, resembling grossly and histologically that seen in other conditions presumably due to a hyperestrinemia. Operative removal of the tumors results in complete regression of symptoms. Geist and Spielman were able to demonstrate large amounts of estrogenic factor in a theca cell tumor. The tumor is usually benign but two cases have been described associated with ascites, and one with metastases, presenting all the clinical and pathologic evidences of malignancy.

Pathologic Anatomy

The theca cell tumors vary in size from that of a peach to neoplasms as large as a good sized melon. They are firm, irregular, solid or partially cystic. A fibromatous-like consistency and appearance is often suggested. A capsule is commonly present and is deficient only when tumor tissue, as in the malignant case described, has perforated it. The cut surface is distinctive; showing lobules of yellowish hue and varying size, separated by strands of fibrous tissue. Cysts, when present, may be small or almost completely replace the tumor, with occasional solid areas or thickened walls. The cysts result from degeneration and necrosis and contain cloudy yellow or hemorrhagic

fluid. The inner cyst wall sometimes has a shaggy appearance. Hemorrhage, necrosis and liquefaction may also be found in the solid portions of the neoplasms. An association with other pelvic tumors has been noted in some cases but no relationship can be drawn between the theca cell tumors and the uterine fibroids or ovarian cysts coincidentally found with them.

Histologically, the theca cell tumors represent a group that may closely resemble fibromas or spindle cell sarcomas, but have a decidedly characteristic histologic structure that distinguishes them from other tumors. The outstanding feature of their histologic composition is the presence of bundles of broad spindle cells, epithelioid in appearance, distributed in an irregular, interlacing manner throughout the tumor, separated by varying sized bands of connective tissue and often containing hyaline plaques. Fine fibrils traverse the intercellular spaces. The cells are usually regular in size, and the nuclei clear and well stained. At times they may appear to resemble luteinized cells. In the malignant type the usual evidences of cell atypism, nuclear variability and mitoses are to be seen. An important diagnostic point is the presence of doubly refractile fat in large amounts within the cells and to a lesser extent in the surrounding connective tissue. The lipoid is not degenerative in origin, but is stored or produced by the cells and probably is in some way related to the presence of an estrogenic hormone which has been demonstrated in the tumor and which presumed to be the important factor in the production of several of the clinical symptoms. The presence of large, fat containing cells, suggesting a resemblance to luteinized theca interna cells or granulosa lutein cells, was noted in the more cellular tumors in some instances.

SUMMARY

The anatomic and histologic characteristics of theca cell tumors are described, together with their distinctive clinical and hormonal features. Descriptions are given of six cases illustrating variations from the more benign fibroma type to the highly cellular and malignant type. A correlation is made between the presence of hormonal changes and the presence of intracellular, doubly refractile fat containing cholesterol and cholesterol esters. It is suggested that some of the ovarian neoplasms previously diagnosed as fibromas or fibrosarcomas may on further investigation prove to be of theca cell origin.

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DISEASE OF THE SPINAL CORD IN PREGNANCY

Myelopathy of Pregnancy, a Clinicopathologic Study

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THE clinical aspects of spinal cord disease of pregnancy have been well defined; however, the pathogenesis of the condition remains obscure. This obscurity is shared by many other complications of pregnancy, clues to the origin of which are lacking. The ultimate solution of the problem waits upon a more complete knowledge of the changes occurring in the organism during pregnancy in disorders usually ascribed to toxemia. Whether the disturbance is metabolic or endocrinologic, or due to some other factor, is at present not determined. Pending the time when such information will have become available, however, pathologic studies of the end-results of these complications of pregnancy may throw some light on the nature of the original disturbance. Pathologic studies of spinal cord disease of pregnancy have been recorded in a very limited number of instances. A number of these cases were reported as "myelitis" of pregnancy. The term, "myelitis," should be used to denote only such lesions of the spinal cord which are truly infectious in origin. As our and the other cases described in the literature are not true instances of "myelitis," we believe that the term, "myelopathy," is more appropriate.

REPORT OF CASES

Case 1.—R. L., aged twenty-six, was admitted to the Montefiore Hospital in November, 1931. At the age of twelve she had developed an osteomyelitis of the right femur with recurrence at the same site when she was twenty-one years of age.

She remained well until August, 1930, at which time she was in the eighth month of her first pregnancy. The day preceding the onset of the illness, she had a slight cold which cleared up within twenty-four hours. The illness was ushered in by pains in the region of the back. A constricting sensation about the abdomen appeared about a week later and then there was difficulty in walking. In a few days she was unable to move her lower limbs. Following this, there occurred loss of sensation in the lower limbs and fecal and urinary incontinence. A cesarean section was performed and the patient was delivered of a normal child.

In November, 1930, the patient was observed at a neurologic hospital in New York City. The neurologic examination at that time showed a spastic paraplegia, with absent abdominal reflexes and a bilateral Babinski toe sign. There was a sensory level at the sixth dorsal segment with complete loss of all forms of sensation below that region. The cranial nerves were negative, except for a poorly sustained nystagmus on left conjugate gaze. Lumbar puncture did not disclose any evidence of a block. The spinal fluid was negative in all respects. Roentgen examination of the spine proved negative.

While the case was considered most likely one of myelopathy of pregnancy, the possibility of an osteomyelitis of the vertebrae was entertained and a laminectomy performed. At operation an atrophic cord, covered by engorged and tortuous vessels, was exposed.

Shortly thereafter the patient was transferred to the Montefiore Hospital. During the next few years of her stay at the hospital the condition of the patient became progressively worse. Examination performed in January, 1934, disclosed the following: The patient was bedridden, suffering from cystitis and from a large bed sore over the left hip joint. She was incontinent of urine and feces. Spontaneous movements of one limb or of both were occasionally noted. A flaccid paraplegia was present, with loss of all the deep reflexes in the lower limbs except the left ankle jerk and both adductor reflexes. The abdominal reflexes were present, but were diminished. The Babinski toe sign was present bilaterally. There was a sensory level at the sixth dorsal dermatome; below this point all forms of sensation were absent. Nystagmus was present on gaze to either side.

In March, 1934, the patient developed meningeal signs. Examination of the spinal fluid disclosed the presence of gram-positive and gram-negative bacilli and other findings indicative of a purulent meningitis. The patient died a day later.

Autopsy.—Gross Examination: Only the spinal cord was removed. The patient had a large decubitus ulcer about six inches in diameter involving the buttocks and sacrum. There was a fistulous communication between this ulcerated area and the subarachnoid space through which a probe could be passed. On applying pressure over the ulcerated area, pus was seen to enter the subarachnoid space.

The spinal cord was considerably swollen. The dura was slightly thickened; the pia-arachnoid, thickened to a greater degree, was adherent to the dura. On cutting the cord, the posterior columns in the cervical region appeared translucent. In the upper dorsal region the gray matter around the central canal was discolored. At about the third and fourth dorsal segments there was an area of reddish discoloration in the region of the posterior portion of the gray matter and the ventral portion of the posterior columns. At about the fifth dorsal segment, because of the hemorrhagic appearance of the cord, the outlines of the fiber tracts were obliterated. This reddish discoloration, which extended from the fourth to the seventh dorsal segment, was most intense at the sixth dorsal segment.

Various sections of the spinal cord at this level, below and above it were stained by the myelin sheath and cresyl violet methods. Frozen transverse and longitudinal sections from the same areas were stained by the myelin sheath, Holzer, Sudan III and Bielschowsky methods.

Microscopic Examination.—In the myelin sheath preparation, the sections of the spinal cord between the fifth and sixth dorsal segments showed thickening of the meninges and extensive demyelination of all the fiber tracts (Fig. 1, *D*) with slight sparing of a few of the white fibers in the gray matter (Fig. 1, *D*). In sections at the fourth dorsal segment all the fiber tracts, except for the fibers of the gray matter and for a few fibers bordering the posterior and anterior horns, were completely demyelinated (Fig. 1, *C*). At the first and second thoracic segments there was demyelination of the fasciculi gracilis and cuneatus, the former more than the latter, and of the direct and indirect cerebellar and part of the spinothalamic tracts (Fig. 1, *B*). Sections above this level merely showed an ascending degeneration of the fasciculus gracilis and the spinocerebellar tracts (Fig. 1, *A*). In sections immediately below the complete area of demyelination, there were patchy areas of demyelination of the posterior columns (Fig. 1, *E*) and marked destruction of practically all of the ventrolateral tracts. These had a honeycombed appearance. The ganglion cells showed no pathologic changes. In the Holzer preparation, the fasciculus gracilis on the right side showed an intense area of gliosis (Fig. 2). Slight

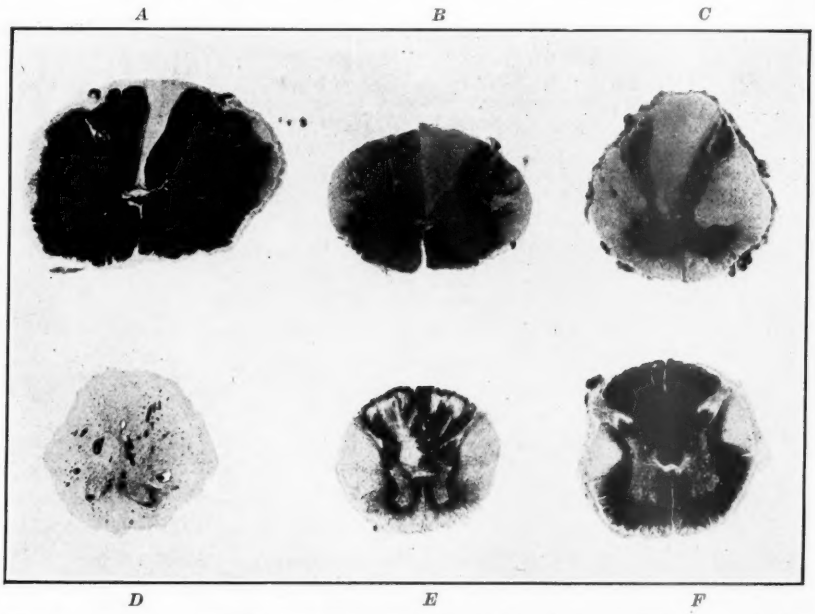

Fig. 1.—Transverse sections of the spinal cord showing complete demyelination of all the fiber tracts from the fourth to the sixth dorsal segment (*C* and *D*). At *D*-¼ segment (*C*) the fibers of the gray matter and those bordering it appeared spared. The sections above this level showed an ascending degeneration (*A* and *B*). In sections immediately below the complete areas of demyelination, there were patchy areas of degeneration of the posterior columns (*E*) and marked destruction of practically all the ventrolateral tracts. In the lumbosacral region there was a descending degeneration (*F*).

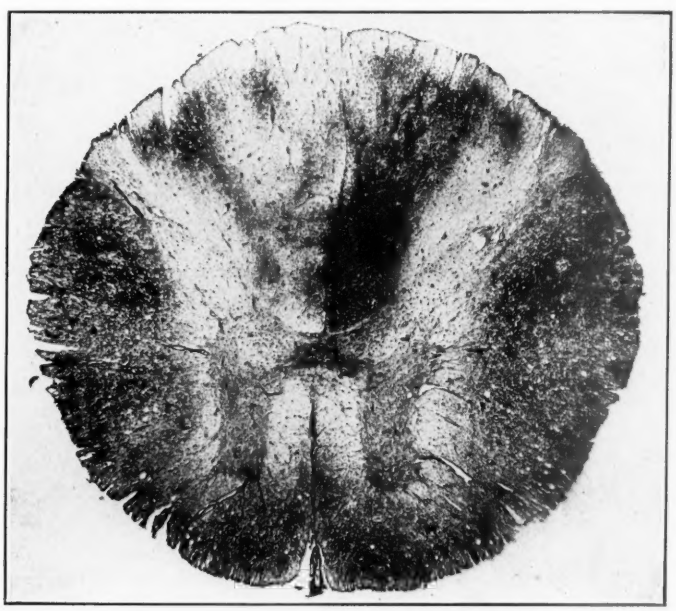

Fig. 2.—Gliosis in area of demyelination. Holzer stain.

gliosis was also found in the lateral and anterior pyramidal tracts. In the lumbosacral region there was a descending demyelination of the lateral pyramidal tracts (Fig. 1, *F*); the anterior pyramidal tracts were only slightly involved (Fig. 1, *F*). With higher magnification the sections at the level of the lesion disclosed a few myelinated fibers within the anterior horns; the other fibers were completely de-

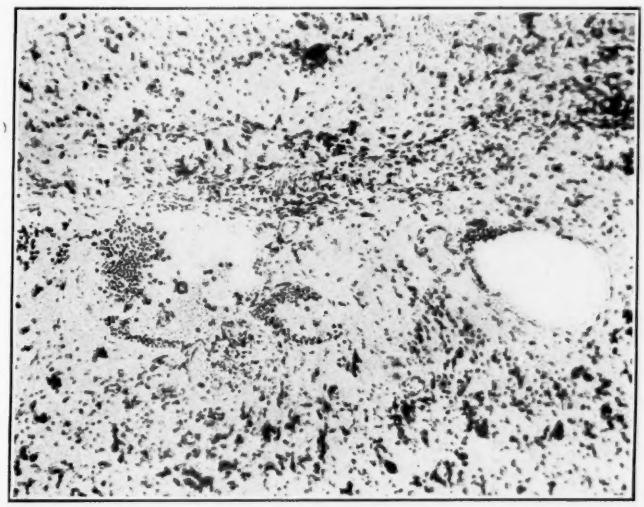

Fig. 3.—Dilatation of vessels lined by a single layer of endothelial cells in area of degeneration. Notice the deposits of iron pigment. Cresyl violet stain. ×50.

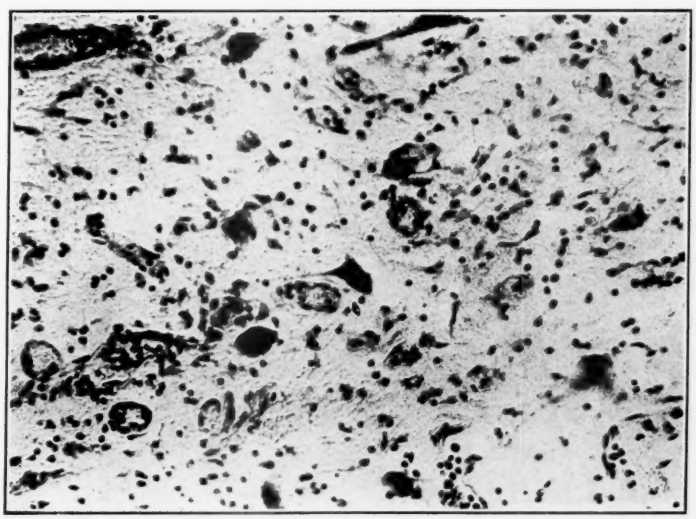

Fig. 4.—Diminution in the number of anterior horn cells. Some appear as shadow cells; others are pyknotic or are completely destroyed. Cresyl violet stain. ×200.

myelinated. The cord at this level did not have a honeycombed appearance but was filled with proliferating and dilated vascular channels (Fig. 3). The gray matter was filled with blood pigment (Fig. 3). Some of the fibers within the anterior roots were slightly demyelinated. In the cresyl violet preparation, the meninges appeared thickened and were filled with polymorphonuclear leucocytes, plasma and

endothelial cells and proliferating arachnoidal and fibroblastic cells. The inflammatory process, athough predominantly limited to the meninges, involved slightly the periphery of the cord and the anterior and posterior roots. Proliferation of the smaller intraspinal arteries in the gray and in the white matter was also noted. The entire transverse section of the cord was filled with plump astrocytes, gemästete

Fig. 5.—Fatty deposits in the cord and in the perivascular spaces. Sudan III stain. ×50.

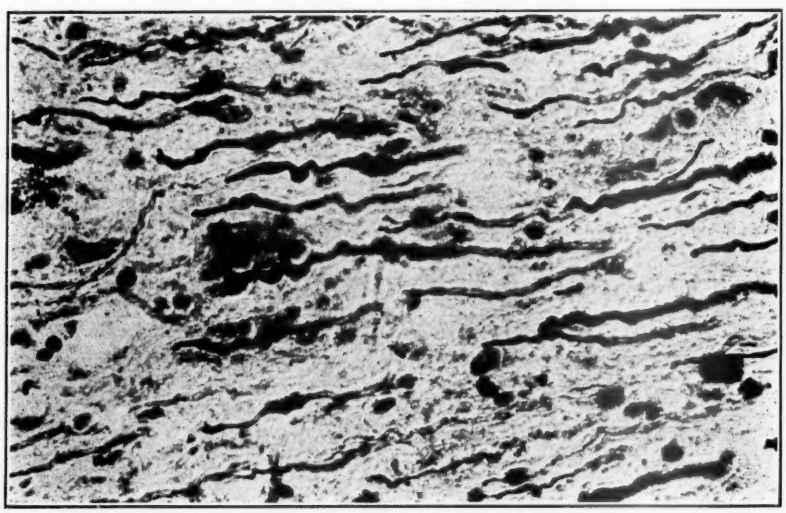

Fig. 6.—Swelling, cork-screw appearance, knoblike projections, beading and destruction of axis cylinders. Longitudinal section. Bielschowsky stain. ×400.

glia cells and occasionally compound granular corpuscles. The ganglion cells of the gray matter were diminished in number and showed various pathologic changes such as shadow cells, complete chromatolysis, shrinkage and pyknosis (Fig. 4). Some of the anterior horn cells were well preserved. In the sections stained with the Sudan III preparation, the areas of demyelination were filled with compound granular corpuscles, loaded with fat. Some of these showed a tendency to collect in the

perivascular spaces (Fig. 5). The gray matter at this level contained small fatty deposits. In the longitudinal sections, the myelin sheaths showed various types of pathologic changes, such as swelling, fragmentation or complete disintegration, while in the Bielschowsky preparation the axis cylinders were either swollen, beaded, tortuous, or fragmented (Fig. 6). Knob-like projections and corkscrew processes were also noted. At the fourth dorsal segment the pathologic process, except for the sparing of the white fibers in the gray matter, was the same. At this level, however, in the cresyl violet preparation, there were no dilated vascular channels and no extravasation of blood or collections of blood pigment. The ganglion cells, although some showed pathologic changes, were in general better preserved. The cord was filled with numerous glia cells of the astrocytic variety; compound granular corpuscles and plump astrocytes were more prominent at the periphery of the cord. In the cresyl violet preparation of the upper thoracic and lower cervical regions, as at the fifth and sixth dorsal segments, there were dilated vascular channels, accumulation of blood pigment, and moderate pathologic changes in the ganglion cells.

COMMENT

The history of an antecedent osteomyelitis and the onset with pain in the back and girdle sensations suggested to some observers an extramedullary process, possibly a recurrence of the osteomyelitis in one of the vertebrae. The roentgen studies, the cerebrospinal fluid findings, and the negative results of laminectomy ruled out this diagnosis. The condition was later considered to be either a vascular myelopathy or a myelopathy due to pregnancy. Clinically, the patient presented a level lesion of the spinal cord, unless one is willing to accept as evidence of dissemination the ocular movements, described at one time as nystagmoid, and later as true nystagmus. In view of the trophic ulcer and the cystitis, it was impossible to determine on clinical grounds whether the progression in the neurologic signs was due to an ascending infection, or to the continued activity of the original noxious agent.

The meningo-myelitic process which developed shortly before death must be considered apart from the main pathologic process which was found at the fifth and sixth dorsal segments. The meningitis was the end-result of the ascending infection from the decubitus ulcer and the fistula which extended into the subarachnoid space. The process at the level lesion was myelopathic in nature and consisted of breaking-down of the myelin sheaths and axis cylinders and a moderate gliosis. The numerous proliferating and dilated vascular channels found at this level and in the upper dorsal and lower cervical regions were the end-result of the destruction of the cord and the attempt at repair. Such a process is not uncommonly seen in myelopathies due to toxic processes or vascular disease. The pathologic picture considered in its entirety conformed to that seen in the toxic myelopathies.

Case 2.—K. N., a primipara, aged twenty-two, was well up to the seventh month of pregnancy in March, 1933. She had been observed every two weeks before that time in a prenatal clinic and found normal in all respects. One morning she felt a sudden pain between the shoulder blades followed soon after by a burning sensa-

tion over the back. A few minutes later she was unable to stand and the lower half of her body felt numb. Sixteen days later a low forceps delivery was carried out. The puerperium was normal. At the maternity hospital, a neurologic examination is said to have disclosed a complete transverse lesion of the cord.

About a month later, she was observed at a neurologic hospital. She then showed a sensory level at the fifth dorsal segment, a paraplegia, bilateral Babinski signs, absent abdominal reflexes, and urinary incontinence. A spinal tap yielded a normal manometric response. The cerebrospinal fluid was normal. A blood count showed a hemoglobin of 58 per cent with 2,860,000 red blood cells. The color index was 1. The smear showed macrocytosis, microcytosis, and poikilocytosis. The bleeding and coagulation time was normal. The test for fragility of the red blood cells was interpreted as showing markedly increased fragility (onset at 0.48 per cent, complete at 0.38 per cent). The gastric analysis showed absence of free hydrochloric acid.

The patient was given iron compounds and responded very well. Her course was complicated by the development of a cystitis, following upon the initial retention of urine and subsequent overflow incontinence. Gradually she improved.

The impression at the time was that the patient had suffered either from an atypical hematomyelia or from thrombosis of the anterior spinal artery.

She was admitted to the Montefiore Hospital in November, 1933. At that time she showed a sensory level at the fourth dorsal dermatome, with diminution of all forms of sensation below that point. The motor status showed a spastic paraparesis in extension with occasional spontaneous flexion movements in the limbs. The deep reflexes were absent and the Babinski sign was bilaterally present. There was persistence of urinary incontinence and of cystitis. The gastric analysis again showed an achlorhydria. The red blood count was now 4,250,000 and the hemoglobin 75 per cent.

The patient was observed for six months at the hospital. She showed signs of improvement during that period. Her status shortly before her discharge disclosed the following findings: The patient was able to stand unsupported and walked with the aid of a cane. There were occasional urgency of urination and incontinence. The motor status was unchanged. Sensation: There was a sensory level for pain and temperature at the fourth dorsal dermatome, the disturbances being less marked than they were. Touch was normally perceived. Vibration was very slightly diminished below the level. Position sense was intact except for occasional errors in the toes of the left foot.

COMMENT

In this case there was, in addition to the neurologic disorder, an abnormal hematologic picture. The absence of free hydrochloric acid and the favorable response to therapy with iron suggested a hypochromic anemia, such as not infrequently sets in during pregnancy. The high color index was not characteristic of this condition, however. It was the opinion of the hematologist that a secondary anemia of pregnancy existed. Whether the same factor which precipitated the myelopathy also was responsible for the abnormal blood picture remains an open question.

In the absence of histologic studies, one can merely speculate on the character of the underlying pathology in this case. A vascular lesion, perhaps a thrombosis of a spinal vessel, was considered by some ob-

servers. That a thrombosis of a spinal vessel produced this picture appears to us extremely unlikely, since the area affected does not correspond to the distribution of any one spinal vessel. A hemorrhage into the substance of the cord is a possibility. As will be pointed out below, however, the occurrence of a hemorrhage into the cord would not necessarily rule out a toxic factor as the primary cause of the disturbance.

DISCUSSION

From the clinical standpoint, the subject of myelopathy of pregnancy was dealt with comprehensively by Hösslin[1] in 1904. He pointed out the necessity of distinguishing a true myelopathy of pregnancy, in which there is a direct causal relationship between the pregnancy and the myelopathy, from other conditions in which the pregnancy is merely coincidental, as in tumors of the spinal cord, or disorders in which the pregnancy acts merely to precipitate or to exacerbate an independent neurologic disease, such as multiple sclerosis. Hösslin cited twenty cases of myelopathy of pregnancy, in five of which the condition recurred in subsequent pregnancies. In one instance, the patient, after three normal pregnancies, suffered five attacks of myelopathy, three of them occurring during pregnancy and two unassociated with gestation. In another case, myelopathy occurred soon after the termination of the sixth pregnancy, in the third month of the seventh pregnancy, and again shortly after the eighth delivery. Similarly, in the case of Windscheid, myelopathy set in after the first delivery, with a recurrence four weeks following the second delivery. Hösslin thought that there was sufficient evidence to indicate an immediate causal relationship between the pregnancy and the myelopathy, and postulated toxins liberated during pregnancy or the puerperium as the responsible agent.

Since Hösslin's contribution, several reports on this subject have appeared sporadically: Rosenberger and Schmincke,[2] Krupp,[3] Schumann and Fist,[4] Good,[5] Marinesco,[6] Alpers and Palmers,[7] Spitzer,[8] Frayman,[9] and Hassin and Ettleson.[10] Spitzer, reviewing the subject in 1932, was able to collect only twenty additional cases since Hösslin's report of twenty cases in 1904.

Clinically, myelopathy of pregnancy is characterized by the following features: The condition may develop in the course of the first pregnancy or only after several normal pregnancies have already occurred; the onset may occur during pregnancy, immediately postpartum, or later in the puerperium. While it may set in during any part of pregnancy, it more commonly occurs during the latter half. The onset may be sudden or gradual. Hösslin expressed the opinion that the more acute the onset, the worse the prognosis, but that this is not invariably so is evident from a study of our own cases in which the more severe and eventually fatal myelopathy followed upon a gradual onset. Usually

there is no rise in temperature, nor are there any other constitutional signs to suggest an infectious process. The neurologic picture varies. There may be signs of a level lesion of the spinal cord, complete or incomplete, or the process may involve the cord diffusely at different levels. Spitzer distinguishes a cervical, dorsal, lumbosacral and disseminated type of myelopathy as well as a funicular type in which the dorsal and lateral columns are involved. In some cases the medulla oblongata has been implicated. The outcome also varies. There may be complete restitution of function, partial recovery, or progression and death, the latter resulting usually from complicating bed sores or cystitis with ascending infection. In Spitzer's review of forty cases, the mortality was 22.5 per cent. The tendency to recidivism in subsequent pregnancies has already been mentioned. In this respect, myelopathy of pregnancy resembles certain other complications of pregnancy, such as peripheral neuritis, lesions of the optic nerve, and icterus neonatorum.

Considerable diversity of opinion exists regarding the underlying etiologic factors in myelopathy of pregnancy. A toxic or an infectious process has been held responsible by some observers. Others favor a vascular etiology without specifying further just what the basis of this vascular disturbance may be.

It seems to us difficult to explain the occurrence of myelopathy of pregnancy on the basis of an infectious process; not because of the customary absence of any history or signs pointing to an infectious disease—since it is well recognized that infections of the nervous system may occur without frank evidence of infection elsewhere in the body—but because of the tendency of a considerable proportion of these cases to recur in subsequent pregnancies. The dramatic improvement that takes place in many of the cases after the pregnancy is interrupted or labor occurs also suggests an intimate relationship between pregnancy and a moderate myelopathy, rather than some fortuitous infectious process. As already indicated by one of us (Davison[14]), mild toxic substances may not produce extensive and permanent damage to the spinal cord.

It is conceivable that the termination of pregnancy suspends the further action of the toxin before irreparable changes have occurred, thus permitting reparative processes to take place. The same objections apply to a vascular etiology. One is led to inquire what kind of vascular disease would make its appearance during a pregnancy, clear up sufficiently following this to allow partial or complete restitution of function, only to reappear in a succeeding pregnancy. In those cases in which a complete or almost complete level lesion exists, it is difficult to understand how occlusion of one spinal vessel can be held responsible, since the cord is supplied by the anterior and posterior spinal arteries as well as by arteries entering at the lateral margins.

To assume that all of the vessels at one level of the cord are simultaneously involved, while vessels at other levels are spared, seems strained.

Accepting, for the moment, the possibility of a vascular etiology, one is also led to inquire whether the vascular disease itself must not be secondary to some other factor since, in these cases, there is no preexisting generalized vascular disease, hypertension, syphilis, cardiac pathology, or any other condition predisposing to a vascular accident.

One argument adduced for the likelihood of vascular disease of the cord is the sharp level lesion that occurs in some of these cases. It is generally held that toxic and infectious processes give rise to more or less disseminated lesions of the cord, and that a sharp level lesion indicates implication of a vessel at that level. The occurrence of a level lesion would not rule out a toxic process, however, if the vascular pathology were secondary to the action of toxins on the vessel wall. In that case, instead of thinking in terms of a vascular *or* a toxic factor, one must think in terms of a vascular *and* a toxic factor.

At the risk of venturing further into fields of speculation, still another possibility that must be entertained as at least a contributory factor in myelopathy of pregnancy is some form of dietary insufficiency. Numerous studies recently made point to a vitamin B deficiency as the underlying factor in gestational neuritis. In these cases hyperemesis is almost constantly present, so that a vitamin deficiency undoubtedly exists. While vomiting is not a factor in the cases of myelopathy of pregnancy, the possibility of a dietary inadequacy is not thereby precluded. During pregnancy the vitamin requirements of the mother are increased. At the same time there may be faulty metabolism and absorption of foods due to the diminished secretion of gastric juices. In experimental avitaminosis, finally, lesions of the nervous system, both degenerative and hemorrhagic, and hence similar to those found in myelopathy of pregnancy, have been observed.

It would seem reasonable to suppose that pathologic studies might shed some light on this obscure problem. That the problem from the standpoint of the pathologist also offers difficulties is soon apparent, since various pathologists, confronted by certain findings in the spinal cord, may offer entirely different interpretations of these findings. It is known, for example, that in toxic myelopathy of infectious myelitis, circulatory disturbances may play a rôle and produce a picture indistinguishable from ordinary vascular myelopathy. In cases in which some pathologists would hold the vascular supply primarily responsible, others might question whether the blood vessels have not been concomitantly affected with the parenchyma, or even secondarily affected after the parenchyma was already damaged. The fact that

the pathologist views the specimen long after the acute process has subsided does not simplify matters. The question also whether a process is infectious or not is often open to dispute. In the chronic phase, perivascular infiltration may have disappeared, while on the other hand, the mere presence of such an infiltration need not indicate a true infectious process but merely a response to tissue damage of any sort, the so-called "symptomatic inflammation" of Spielmeyer. In this connection, one of us (Davison[15]) has pointed out the need for caution in interpreting perivascular infiltrations as evidence of an inflammatory process, since special histologic studies have shown that cells considered as lymphocytes may really be fat-laden glia cells (compound granular corpuscles).

Bearing all these difficulties in mind, we have ventured an interpretation of the histopathologic findings in our case and concluded that the process is toxic in nature. At the same time we envisage the possibility that some form of vitamin deficiency may be at least a contributory factor.

The number of cases of myelopathy of pregnancy that have been studied with sufficient care to serve as a basis of comparison with our case is exceedingly small. For this reason it is advisable to review them briefly.

In the case described by Hamill,[12] the disease occurred in a primipara fourteen days after labor. The lower limbs were first involved, later the upper limbs. There was a sensory level slightly above the umbilical region, with anesthesia below that point. The patient died five days after the onset, in coma. Postmortem examination disclosed an acute diffuse hemorrhagic "myelitis," the lower dorsal and upper lumbar regions of the cord being most affected. In these regions the nerve fibers had disappeared; the cells in the anterior horns of the gray matter were swollen and shapeless. Rosenberger and Schmincke[2] described a case of "myelitis" occurring in a primipara during the third month of pregnancy. At first there was involvement of the lower limbs; this later spread to the upper limbs. There were a sensory level at the region of the nipples, bilateral pyramidal tract signs, and vesical disturbances. Later, bulbar signs appeared. The histologic study of the spinal cord disclosed disseminated lesions of a "parenchymatous degenerative" nature, more marked in the cervical and less marked in the thoracic and lumbar segments. Both the gray and the white matter were affected. Bauch[13] described the case of a primipara who, eight days after labor, developed bulbar signs in the form of dysarthria and dysphagia followed shortly by diplopia. Death occurred within a few days. Histologic study disclosed perivascular infiltrations of lymphocytes in the medulla oblongata and in the quadrigeminal plate. In the upper cervical region of the spinal cord, similar perivascular cuffing was present in the gray and white substance and in the meninges. The ganglion cells were unevenly colored, but did not show frank signs of degeneration. Hassin and Ettleson[10] more recently reported a case of myelopathy occurring during pregnancy in a girl of nineteen. A history of antecedent syphilis and the occurrence of an upper respiratory infection at the time of onset of the myelopathy were complicating factors. The neurologic status showed a level lesion with a flaccid paraplegia; pain and temperature sensations were lost up to the level of the umbilicus; there was also vesical incontinence. Infection from bed sores led to death. There was no glossitis nor a blood picture

characteristic of pernicious anemia. A gastric analysis was not performed. Histologic study showed changes in the lateral columns with only mild involvement of the posterior columns of the cord. "The changes were not those of syphilis or of inflammation. . . They were degenerative, of the type observed in subacute combined degeneration of the spinal cord; they resembled nothing else." The authors thought the picture of subacute combined degeneration of the cord found in this case might be a manifestation of a toxemia of pregnancy. Of these cases, the one reported by Bauch clinically and pathologically suggests the diagnosis of a bulbar poliomyelitis. In the three remaining cases the pathologic process was degenerative or hemorrhagic in nature. These resembled in many respects our first case. The etiology was most likely toxic in nature.

SUMMARY AND CONCLUSIONS

One case of myelopathy of pregnancy, studied clinicopathologically, and another observed clinically, are reported.

A survey of previous histologic reports has shown that the underlying pathologic process is degenerative or hemorrhagic in nature.

Reasons for believing that myelopathy of pregnancy may be due to some toxic factor, the exact nature of which remains as yet undetermined, and that vitamin deficiency may play a contributory rôle in the production of the disease, have been presented.

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Rock, Reboul, and Wiggers: Detection and Measurement of Electrical Concomitant of Human Ovulation, New England J. Med. **217:** 655, 1937.

Burr, Hill and Allen as the first demonstrated by means of a vacuum-tube potentiometer, in the rabbit, a change in the electrical potential immediately preceding the rupture of a ripe follicle. Reboul, Friedgood, and Davis confirmed these significant observations on rabbits.

Rock, Reboul, and Wiggers describe in this paper in great detail a parallel observation made on a regularly menstruating woman. Histologic examination of follicular tissue and endometrium obtained during a required laparotomy proved that voltage changes, quite similar to those observed in the ovulating rabbit, also in this patient seemed dependent upon the rupture of a mature follicle.

Hugo Ehrenfest.

FUNCTIONAL UTERINE BLEEDING WITH SPECIAL REFERENCE TO THAT ASSOCIATED WITH SECRETORY ENDOMETRIUM

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FROM time to time there has appeared in the literature evidence which would seek to explain functional uterine bleeding on a basis other than that of endometrial hyperplasia. Whether or not such an entity or entities exist is a matter of controversy. Graves[1] states that "typical dysfunctional metrorrhagia is almost always associated with endometrial hyperplasia." Novak[2] agrees and says that "histologic examination of the endometrium in cases of functional hemorrhage, almost always reveals the picture designated as hyperplasia of the endometrium."

On the other hand there have been a series of papers tending to show that functional uterine bleeding can occur in the absence of an endometrial picture of hyperplasia. However, there is a conspicuous absence of agreement among these authors as to the nature of the abnormalities (Table I).

TABLE I. THE INCIDENCE OF FUNCTIONAL UTERINE BLEEDING ASSOCIATED WITH HYPERPLASTIC AND NONHYPERPLASTIC ENDOMETRIUM

	NO. CASES	HYPERPLASIA		NONHYPERPLASIA	
Kaufmann and Hoeck, 1926[3]	133	45	43%	75	55%
Fluhmann, 1929[4]	90	49	54%	41	46%
Anspach and Hoffman, 1934[5]	97	53	55%	44	45%
Keene and Payne, 1934[6]	500		23%		77%
Traut and Kuder, 1935[7]	100	68	68%	32	32%
Hamblen, 1936[8]	358	102	28%	256	72%
Present study, 1937	83	52	63%	31	37%

The great variation in the incidence of hyperplasia probably depends on individual opinion in diagnosis of hyperplastic endometrium and the variation in types of cases included in the nonhyperplastic group.

Pankow[9] in 1924 described 3 cases of abnormal bleeding in which he thought there was a characteristic endometrial picture. Here the endometrium had no epithelial surface. The stroma was compact and infiltrated with round cells and blood. The glands were collapsed, but there was no evidence of secretion. Pankow supposed that there was a delay in the regeneration of the endometrium.

In the study of Kaufmann and Hoeck, published in 1926, the pathologic findings of the endometrium in 133 cases with abnormally profuse bleeding are described in detail. They point out that there is no characteristic clinical history associated with any of the pathologic pictures presented. Hyperplasia was found in 58 cases. The remainder are grouped into 6 types as follows:

1. Six cases showed abnormal shedding of the endometrium. The surface is irregular and humpy. The stromal cells are compact and the nuclei are small. The

glands assume bizarre forms and are many times star-shaped. The lumina are filled with secretion. The protoplasmic edge of the epithelium is irregular, the nuclei are at the base of the cell and glycogen can be stained in the secretion and in the cells. The authors consider that there is an incongruity between the actively functioning glands and the inactive appearing stroma.

2. In 14 cases the diagnosis of "functionless endometrium" is made. Here the endometrium is covered with a smooth surface. The glands are procumbent, but without irregularity in form. The epithelium is cylindrical, the protoplasmic edge is sharp and the protoplasm itself is dark and not translucent. The nuclei occupy the greater part of the cell. The stroma is rich in nuclei and fibers. The capillaries are abnormally dilated. On the one hand this is differentiated from interval endometrium by the delicately active stroma and clear cytoplasm of the latter. On the other hand it is differentiated from atrophic endometrium by the general shrinking of the stroma of the latter and the atrophic appearing nuclei. In this group of cases, the correlation between the ovarian cycle and that of the uterus seems to be lost and there is no evidence of any cyclic activity on the part of the endometrium.

3. In 20 cases, most of them at the menopause, a diagnosis of atrophic endometrium is made. Here there is a generalized shrinking process of the stroma with collagen fibers and shrunken nuclei. The glands are scattered irregularly through the rigid stroma.

4. In 13 cases the endometrium is described as normal except for congestion. However, in only two cases could a cause for the congestion be discovered. In these the patients were suffering from myocardial insufficiency. A restoration of circulatory compensation corrected the irregular bleeding.

5. In 18 cases the endometrium is considered normal. The phase is not described.

6. In 4 there was a marked chronic endometritis.

It will be noted that Kaufmann and Hoeck have drawn fine pathologic lines. In the present study this classification was kept in mind, but it must be said that it was difficult to identify these finely differentiated endometrial types.

Baniecki,[10] from the same Berlin clinic as the above authors, published a series of cases (32) with the characteristic endometrial findings of irregular shedding as originally described by Kaufmann and Hoeck. The clinical histories and the microscopic findings with several photomicrographs are presented.

In this country Fluhmann found that there was little correlation between any one type of bleeding history and a special type of endometrium. In 90 cases Fluhmann found 6 endometrial pictures: hyperplasia, 54 per cent; endometrial polyp, 3 per cent; simple hypertrophy of the endometrium, 2 per cent; endometritis, 8 per cent; atrophy, 6 per cent; normal endometrium, 27 per cent. In this latter group no statement is made of the endometrial phase. In contradistinction to Kaufmann and Hoeck and to Baniecki, Fluhmann did not diagnose irregular shedding, functionless endometrium or edematous endometrium although there is no reference to either of these papers in Fluhmann's article. In over 85 per cent of his cases of functional bleeding, the endometrium was found to be either hyperplastic or normal. As noted above, Fluhmann included endometrial polyps and endometritis in his series of functional bleeding. Many authors would exclude these from such a group and if this were done, in over 91 per cent of his cases the endometrium would be either normal or hyperplastic.

Anspach and Hoffman in 1934 described the endometrial findings in 97 cases of functional bleeding. In agreement with practically everyone who has published on this subject, they found that there was no correlation between any one type of bleeding and the endometrial picture; 31 are associated with premenstrual endometrium. This high percentage (70 per cent) may be due to the fact that care

was taken to curette before the expected period of bleeding. Where bleeding was irregular, curettage was performed irrespective of the flow. The remaining cases showed either normal interval or atrophic endometrium. These workers noted some variation in the phase of the endometrium in different portions of the scrapings, but did not consider them significant enough to group together as an entity.

Keene and Payne also in 1934 reported the findings in 500 cases of functional uterine bleeding. All types of bleeding history are represented. Table II from their paper summarizes their results. There was a 23 per cent incidence of hyperplasia in the whole series. Phases of the normal endometrium are not reported.

TABLE II

	NO. CASES	NORMAL ENDOMETRIUM	HYPERPLASIA	INSUFF. TISSUE	EDEMATOUS ENDOMETRIUM	CHRONIC ENDOMETRITIS
		%	%	%	%	%
Menorrhagia group	190	76	12	10	1.5	0.5
Metrorrhagia group	310	56	30	10	1.5	2.5

Traut and Kuder in 1935 described 11 patients, the endometrial findings in whom corresponded with that described by Kaufmann and Hoeck and enlarged upon by Baniecki and called by them irregular shedding of the endometrium. Traut and Kuder state, "it would seem probable that in this type of menorrhagia we may be dealing with nothing more complicated than a very much prolonged menstrual period." With this we fully agree and would further point out that the description given by them and by the earlier workers could apply to endometrium obtained from a normally menstruating uterus. In our opinion there is nothing characteristic about this endometrium which would allow it to be set apart as a pathologic entity.

In this same paper Traut and Kuder describe a series of 21 cases of a new pathologic group and called by them irregular ripening of the endometrium. The pathologic point of departure is a variability of the phases of the endometrium in different areas of the same uterus. In order to make this diagnosis, both a secretory and nonsecretory phase must be identified. While the present study is primarily concerned with functional uterine bleeding from secretory endometrium, we have encountered only minor degrees of variability. Many further observations must decide the significance of this possibility. In several cases we have studied, in which the diagnosis of irregular ripening of the endometrium was considered, we could not convince ourselves that relatively large bits of tissue showing interval or mild hyperplasia in otherwise secretory endometrium were not fragments of endometrial polyps. The diagnosis of endometrial polyp from curettings is not made as frequently as one might suppose, considering the not infrequent finding of polyps in uteruses where the whole specimen is available for study.

Hamblen has recently attempted a functional classification of uterine bleeding from a histologic examination of the endometrium in correlation with clinical data and therapeutic response. His classification is based on the theory that menstrual bleeding occurs during cyclic phases of relative estrin deficiency. He likewise assumes that irregular and often acyclic phases of relative estrin deficiency occur resulting in functional irregularities.

Table III, compiled from Hamblen, summarizes the results in 358 patients divided according to whether or not the patient was bleeding when the specimen was obtained.

A given case is diagnosed as belonging to any of these functional classes according to its endometrial pattern. Anestrin phase is diagnosed from atrophic endometrium, regular estrin phase from postmenstrual or interval endometrium. An irregular pattern with individ-

TABLE III

	BLEEDING	NOT BLEEDING
Hypoestrin or anestrin phase	38	38
Regular estrin phase	6	10
Phase of irregular estrin action	34	60
Phase of prolonged acyclic estrin action	68	34
Progestational phase following irregular estrin action	5	35
Progestational phase following prolonged acyclic estrin action	4	9
Progestational bleeding phase with irregular or incomplete tissue shedding	8	—
Progestational bleeding phase with usual tissue loss	9	—

ual variations in different portions of the endometrium is thought to result from "irregular" estrin action. Prolonged estrin action yields classical endometrial hyperplasia. Patchy progestational change in either of the latter two types places that case in the appropriate group. The two progestational bleeding phases depend upon whether or not there is abnormal tissue loss.

A functional classification of uterine bleeding is very desirable, and useful as a working guide to therapy. However, before such a classification is finally worked out, many more endocrinologic observations must be made. The assumption of what is happening to the hormones by an examination of the endometrium may be misleading.

FUNCTIONAL BLEEDING WITH SECRETORY ENDOMETRIUM

A consideration of the literature serves to show the variation in the endometrial findings especially those cases not associated with hyperplasia. As pointed out some authors deny the existence of functional bleeding except in the presence of endometrial hyperplasia. Therefore as distinct from hyperplasia we have studied a series of 41 cases from the records of the Gynecological Department of the Johns Hopkins Hospital in which functional uterine bleeding seems to be associated with secretory endometrium. As far as can be determined by bimanual and speculum examination all local causes such as cervical polyps, myomas, carcinoma, inflammatory conditions of the uterus and adnexa were excluded. Two cases in which small cystic ovaries were palpated and which were available for examination are included. Cases with hypertension were not included.

INCIDENCE

From histologic examination of the endometrium, we have found it impossible to group all cases into those associated with hyperplasia or those associated with secretory endometrium. There is a group remain-

ing diagnosed as postmenstrual, interval or atrophic. It is not felt that this residue should be subdivided as entities for it is clear that some cases in this group may in reality belong to either of the other two. Postmenstrual or interval endometrium may be found in a given case which at a previous curetting had shown classical endometrial hyperplasia. This does not necessarily mean that there has been a change in the endocrinologic background. This finding would be possible if the characteristic hyperplasia pattern had been shed and there had not yet been time to rebuild beyond the normal appearing postmenstrual or interval pattern. On the other hand it is quite possible that these same cases might, had they been curetted at another time, show secretory change. Atrophic endometrium is normal after the menopause. Many authors have made this diagnosis in abnormally bleeding women during active menstrual life. When atrophic appearing endometrium is found under these conditions it may represent scanty material obtained from the basalis and perhaps a little from the functionalis and thus the tell tale part of the endometrium has already bled away, so that here too these cases may in reality belong to either the hyperplasia or secretory group.

With these facts in mind a consecutive series of 83 cases of functional bleeding was studied, in order to determine the incidence in this clinic. This series of 83 cases is separate and distinct from the 41 cases chiefly studied in this report. The following diagnoses were made:

1. Endometrial hyperplasia	52	63%
2. Secretory endometrium (late interval, premenstrual, menstruating)	14	17%
3. Belonging to neither (1) or (2) (postmenstrual, interval, atrophic)	17	20%

AGE OF OCCURRENCE

Functional uterine bleeding with secretory endometrium may occur almost at any time from the menarche to the menopause. The extremes in the series under analysis are seventeen and forty-nine. It should be pointed out that these figures apply to the ages of the patients when they were seen at the hospital and not to the age when abnormal bleeding began. This latter age can easily be determined from a study of the clinical history. It is obvious that these two figures in any one case may differ by several years. Table IV shows the number of cases by five-year intervals both on admission to the hospital and at the onset of abnormal bleeding.

This reveals an interesting clinical fact, namely that over half the cases (61 per cent) occur between the ages of twenty-five and thirty-nine, in sharp contrast to the age incidence of hyperplasia bleeding which occurs at the extremes of menstrual life and especially over forty. In Schroeder's series of hyperplasia, 77.8 per cent are over the age of

forty. On the other hand 76.6 per cent of this series are below the age of forty. Taking into consideration the much more frequent actual occurrence of hyperplasia, we see that if a woman under the age of forty is found to have functional uterine bleeding there is almost an even chance that secretory endometrium will be found. However, if she is over the age of forty the chances are overwhelmingly in favor of hyperplasia.

TABLE IV

AGE	NO. CASES UPON HOSPITALIZATION		NO. CASES AT ONSET OF SYMPTOMS	
Below 15	0		3	7%
15-19	2	5%	4	10%
20-24	4	10%	3	7%
25-29	8	18%	7	16%
30-34	7	16%	9	25%
35-39	10	28%	7	16%
40-44	7	16%	6	14%
45-49	3	7%	2	5%
	41		41	

CLINICAL HISTORY

There is no characteristic menstrual history although there are three more or less distinct types of alteration:

1. Increase in amount and duration of flow with normal interval with or without intermenstrual bleeding.
2. Increase in amount and duration of flow with shortened interval with or without intermenstrual bleeding.
3. Irregular bleeding.

1. The simplest alteration is an increase in the length and amount of flow with no alteration in the interval. Twenty patients fall into this group. For this study no patient was included that had bled less than eight days. This excluded a large series of borderline cases where periods were increased from three to four days to from five to seven days and a group in which the patients complained of an increase in flow with a normal duration. It should be pointed out that although the alteration was considered too trivial to be included in the study, it was considered important enough by the patient to consult a physician. Such cases perhaps represent the earliest alteration from normal. Seven patients with simple menorrhagia also complained of intermenstrual bleeding.

2. In 10 patients the interval was shortened, in one patient being fourteen days. In the majority of these menstruation was also prolonged.

3. Eleven patients had irregular bleeding, one as long as forty-two days. In many of these the first alteration was menorrhagia, then shortening of the interval and finally complete derangement of the cycle.

ENDOMETRIAL FINDINGS

Hitschmann and Adler were among the first to correlate the cyclic changes in the endometrium. These authors suggested a division of the menstrual cycle into 4 phases and with modification this division is used here. The interval phase is considered to have two subdivisions. In *early interval,* the surface epithelium is columnar, the glands are still relatively straight and the stroma compact. There is no evidence of a secretion. In *late interval,* the surface epithelium is still columnar and tall. The glands are wider and more tortuous and the epithelium of the glands has begun to show evidence of secretion as droplets in the cytoplasm. No endometrium can properly be considered as late interval unless evidence of secretion is found. Such endometrium would usually be present, from soon after ovulation until the premenstrual change takes place, this happening according to Novak about the beginning of the last week of the cycle.

In the premenstrual phase the surface epithelium is intact in the curettings and retains its high columnar form. The glands are extremely convoluted with a general corkscrew pattern. The lining cells are now quite flat, the inner border is irregular and the cytoplasm seems to melt into the gland lumen. The stroma cells are much larger and may resemble the early decidual cells of pregnancy. This resemblance may be so great that various authors have referred to them as pseudodecidual cells.

In menstruating endometrium the surface epithelium is normally absent. The glands are collapsed. The lining cells are flat and still show by the irregular border and cytoplasmic droplets the evidence of secretion. The stroma is shrunken, the cells are small and there is a general influx of wandering cells.

In the 41 cases of this series, the endometrium obtained from curettings showed late interval in 10 instances, premenstrual in 24, menstrual in 7, while in 6 there were minor variations as will be described. Some cases have more than one curetting. The presence or absence of bleeding as well as the time of curettage in relation to the time of the menstrual cycle is of great importance in interpreting the endometrial findings. In some cases the bleeding is so irregular that the fundamental menstrual rhythm cannot be determined.

In the 10 cases in which a clinical history of shortened menstrual interval was obtained, the diagnosis of late interval endometrium was made in 8 patients and premenstrual in 2. In all of these, in addition to the shortened interval, there was menorrhagia and in 2 instances there was a slight amount of intermenstrual bleeding. When the findings are considered in relation to the histories of the individual patients, it seems that the interval has been shortened by bleeding occurring from endometrium which had not yet had time to undergo change into premenstrual phase. That this probably happens is illustrated by a forty-six-year-old patient who for six months had been having menorrhagia every three weeks. The patient was curetted on the first day of bleeding, and late interval endometrium was obtained.

There are 20 patients with menorrhagia and a normal interval, among whom are 7 associated with intermenstrual bleeding, not severe enough, however, to mask

the fundamental menstrual rhythm. Six were curetted in the intermenstrual interval. In each of these, normal secretory endometrium was obtained, corresponding to the calculated day of the cycle. One of the patients of the latter group, K. M. (K62153), appeared in the gynecologic dispensary June 25, 1936, complaining of very profuse menstrual periods. Since 1930 a curettage had been done 3 times and also a right oophorectomy and suspension with only temporary relief. Report from the hospital where laparotomy was performed stated that the right ovary was "cystic." It is not known if a pathologic examination was made. The flow was now so profuse that the patient, who was a stenographer, could not work and had to remain in bed during the monthly flow. The physician who saw this patient in the dispensary made a tentative diagnosis of endometrial hyperplasia. Suction curettage, on the twenty-fifth day of the cycle, revealed well-developed premenstral endometrium.

Six patients were curetted while bleeding. One, curetted on the second menstrual day, showed menstruating endometrium. Two others, one on the first and one on the second menstrual day, showed normal premenstrual findings. Of special interest are the three remaining patients, curetted on the ninth, thirteenth, and twentieth days of a prolonged profuse period. In each case secretory endometrium was obtained.

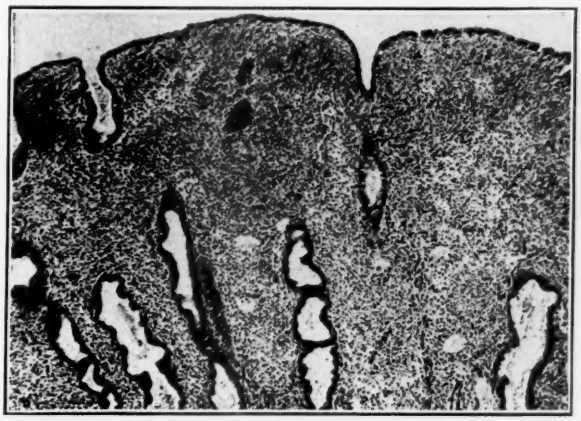

Fig. 14.—(U59694.) Curettings obtained on twenty-first day of continued menstrual period showing interval pattern with secretory epithelium. ×75.

So far it has been assumed that although there has been abnormal bleeding, the endometrium has continued to undergo its usual cycle. However, a consideration of the following case, in which secretory endometrium was obtained on the twentieth day of bleeding suggests an alternate possibility:

A thirty-five-year-old woman (U59694) entered the hospital Dec. 20, 1934, complaining of lower right quadrant pain and menorrhagia. For the past few months periods had been lasting two or three weeks, interrupted occasionally by a period of normal duration. The lower right quadrant pain had been growing steadily worse. Last menstrual period November 30 to present. However, no note is made of bleeding at the ward examination, and it is definitely stated at the time of curettage on December 21 that no bleeding was present, so that the period may have ended. Previous menstrual period October 22 to November 1. Ether examination revealed normal pelvic organs except for a small cystic ovary on the right. As this was not thought to be large enough to cause the patient's lower right quadrant pain, only a curettage was done. The endometrium obtained was markedly secretory, al-

though it was not typical late interval or premenstrual (Fig. 1A). The general pattern was that of interval with slightly tortuous glands, but without the corkscrew premenstrual pattern. The gland cells, however, showed very marked secretory activity. Postoperatively the patient had no further bleeding, but still complained of lower right quadrant pain. Cystoscopy revealed no cause for this in the right kidney or ureter. Accordingly, because of the above-mentioned cystic ovary, laparot-

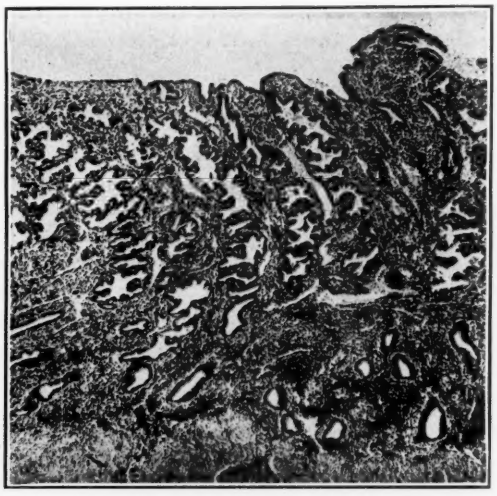

Fig. 1*B*.—(U59694.) Endometrium twenty-seven days after curettings shown in Fig. 1*A*. Endometrium only 3 mm. thick and very compact. Cork-screw glands and active secretion. ×60.

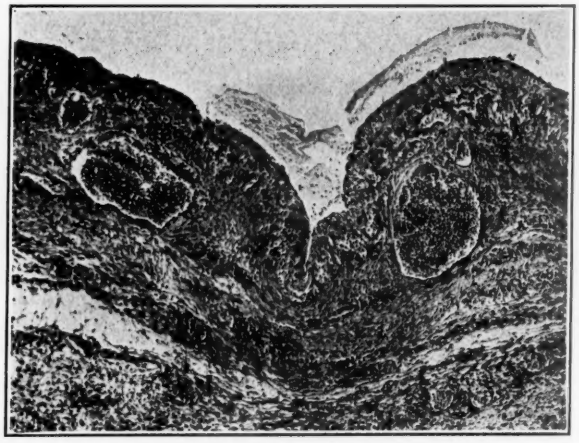

Fig. 1*C*.—(U59694.) Wall of corpus luteum cyst associated with irregular bleeding from secretory endometrium. ×75.

omy was carried out Jan. 17, 1935. The uterus was found to be normal, the left tube and ovary had been removed. There were numerous adhesions binding the right tube and ovary to surrounding structures. There was a right hydrosalpinx about 1 cm. in diameter and in the right ovary was a "small" cyst with a thin yellowish lining. Sections showed normal uterine muscle. The endometrium was not over 3 mm. in depth. The glands had a well-marked corkscrew pattern and

secretory epithelium (Fig. 1B). Section of the right ovary revealed a corpus luteum cyst lined with several layers of lutein cells (Fig. 1C). Diagnosis: Normal uterus, premenstrual endometrium, hydrosalpinx right, corpus luteum cyst of ovary, right. The possible interpretation of this finding will be considered below.

Of the 7 cases of simple menorrhagia associated with intermenstrual bleeding none were curetted while having a menstrual period. Two of these, one on the thirteenth and the other on the twenty-first day showed late interval endometrium. The others, falling between the twenty-second and the twenty-seventh days, showed premenstrual changes.

In one of this latter group there was an associated corpus luteum cyst. The patient (U39499) complained of menorrhagia and slight intermenstrual bleeding of two years' duration. A small mass about 5 cm. in diameter was palpated in the right adnexal region. This was thought to be inflammatory. On the twenty-fourth

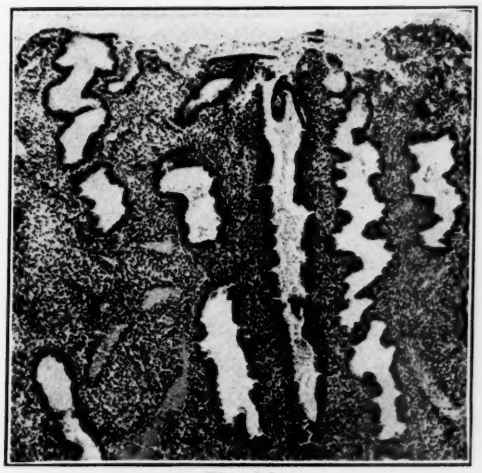

Fig. 2A.

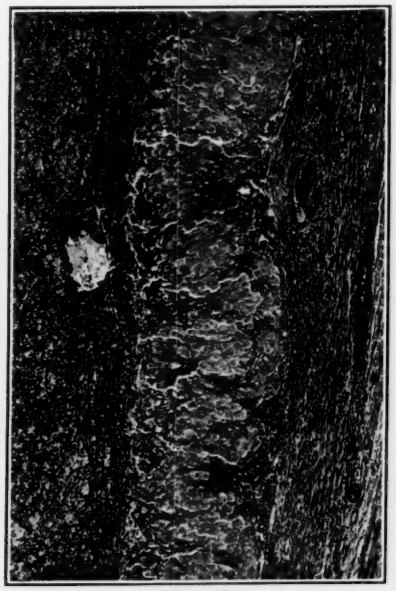

Fig. 2B.

Fig. 2A.—(U39499.) Curettings obtained on twenty-fourth day of cycle. Patient complained of menorrhagia of two years' duration. ×75.

Fig. 2B.—(U39499.) Wall of corpus luteum cyst associated with abnormally profuse bleeding from secretory endometrium. Many layers of lutein cells inner border of which is lined by fibroblasts. Coagulated fluid in lumen. ×75.

day of the cycle a curettage and laparotomy were performed. Late interval endometrium was obtained (Fig. 2A). The mass on the right proved to be a cyst in the right ovary measuring 4 cm. in diameter and showing a lining of lutein cells (Fig. 2B).

There were 11 patients bleeding so irregularly that the fundamental menstrual rhythm was obscured. All of these were bleeding when curetted. In 3 instances the diagnosis of menstruating endometrium was made. In the remaining 8 patients although active bleeding had been going on up to thirty-four days, normal premenstrual tissue was obtained. Apparently bleeding was occurring from endometrium which was not being shed as in normal menstruation or at any rate was not being shed to the extent which occurred in normal menstruation.

DISCUSSION

We may summarize the pathologic findings in this series very briefly by stating that functional uterine bleeding may occur from tissue which is indistinguishable from normal secretory endometrium. All secretory phases are represented, late interval, premenstrual and menstrual. An important question immediately arises. Does the presence of secretory endometrium necessarily prove that prolonged estrin action is not an associated condition? This is important because some writers have contended that almost invariably with functional uterine bleeding there is found endometrial hyperplasia thus implying abnormal estrin action. Based on the observations of Schroeder,[11] Novak and Martzloff,[12] Burch and others,[13] it is now generally thought that hyperestrinism and a suppression of ovulation are associated with a pathologic picture of endometrial hyperplasia. Might it not be possible to have functional uterine bleeding associated with hyperestrinism without the suppression of ovulation? A direct attack upon this point would be the determination of blood and urinary estrin in a series of cases of this type. So far as we know this has not been done.

It is likewise impossible to determine this point by an examination of the endometrial tissue. At first thought one might expect the tissue from such a condition to show an excessive proliferative pattern in addition to secretion; in other words the tissue might be expected to have the general pattern of hyperplasia, but exhibiting secretion. However, this is probably not the case, for in early pregnancy where there is a physiologic excess of estrin, the endometrium shows an exaggerated corkscrew pattern which does not resemble the general pattern of hyperplasia. There is then no evidence at present on this important point, and these cases must be further studied from this point of view.

A second important question arises: In these cases does the endometrium continue to undergo a cycle or is there a persistence of the secretory phase for a long period of time? If this latter possibility were correct, we would have a syndrome which might be comparable in its pathologic anatomy and physiology to endometrial hyperplasia. Unfortunately here too there is no conclusive evidence. However, from the material of this study, there is suggestive evidence which might support either point of view. Indeed there may be represented cases of each type.

The women complaining of simple menorrhagia, that is, those with increased menstrual flow with a normal interval and even those with a shortened interval, might be considered because of the regular periodic nature of their bleeding, to indicate a cyclic activity on the part of the endometrium. This is by no means certain, for periodic bleeding does not necessarily imply cyclic endometrial change. Martzloff, Novak and others have reported cases of endometrial hyperplasia with regular

normal periods. However, this is probably the exception rather than the rule and regular periodic bleeding most likely occurs more often from cyclic endometrium.

On the other hand, there are two points which might indicate that there is a persistence of secretory endometrium for a long period of time. First, there are 11 patients with a history of irregular bleeding obscuring the menstrual cycle. In 8 of these normal premenstrual endometrium was obtained from patients who had been bleeding for various lengths of time from twenty to thirty-four days. This may mean that the premenstrual endometrium had been present during the bleeding and perhaps even before, because in almost all patients there was a history of irregular menses immediately preceding the prolonged bleeding which was interrupted by the curettage.

Second, those patients with corpus luteum cysts may have had a persistence of secretory endometrium. It may be that these cysts secrete progesterone for a long period of time and thus maintain secretory endometrium. In such a case mentioned above, secretory endometrium was obtained after the cessation of a prolonged menstrual period.

It is possible to decide this important question of whether or not the endometrium continues to undergo its cycle by securing an endometrial biopsy once each week for several consecutive weeks. This can easily be done by an endometrial biopsy punch or a suction curette, taking care each time to secure a specimen of tissue from a different portion of the uterus. Such a series is now under consideration and will be reported in a later communication.

The fact that secretory endometrium is found in the presence of functional uterine bleeding might indicate that the fault lay in the function of the corpus luteum. The precise nature of this possibility is a matter of even greater speculation. Bleeding in the presence of progesterone might be considered to be at variance with the literature for Corner[14] and others have demonstrated in the monkey that even small amounts of progesterone are effective in postponing the onset of an expected menstrual period and have shown that bleeding invariably occurs five or eight days after its withdrawal. Furthermore, it has been shown[15] that progesterone is effective in preventing bleeding following the withdrawal of estrone and many authors have suggested its use in controlling functional uterine bleeding especially that associated with hyperplasia. However, it might be possible that prolonged bleeding from secretory endometrium would occur if progesterone were gradually withdrawn. This possibility also does not seem to be likely, for Hartman and Markee[16] in work which has not yet been published have shown in the monkey that bleeding does not occur under these conditions and have demonstrated that the endometrium undergoes an involution without shedding or bleeding. The unraveling of this conflict must await future observations. However, the conflict may be more apparent than

real for, although we know that bleeding will occur following the withdrawal of esterone and progesterone, we do not know if this is the important factor in bleeding or whether this is but a link in a much more complex chain. There might even be some positive factor in bleeding having no direct relation to the phase of the endometrium as was suggested by the work of Hartman, Firor and Geiling[17] and recently championed by Wilson and Kurzrok.[18]

It seems clear that functional uterine bleeding can be associated with secretory endometrium, and it may be possible that, in at least some cases, there may be a persistence of secretory endometrium for a long period of time.

SUMMARY

1. It has been too widely accepted that functional uterine bleeding is almost invariably associated with endometrial hyperplasia, but in our experience with 83 consecutive cases about 14 per cent are associated with secretory endometrium.

2. Forty-one cases of functional uterine bleeding associated with secretory endometrium are studied in detail. (a) In most cases the complaint was simple menorrhagia. (b) Secretory endometrium was found during bleeding which lasted for as long as thirty-four days, and it was also found after prolonged bleeding associated with corpus luteum cysts, suggesting the possibility that with functional uterine bleeding secretory endometrium may persist for a long period of time.

NOTE: I wish to express my appreciation to Dr. Thomas S. Cullen, Dr. Carl G. Hartman, and Dr. Richard TeLinde for many valuable suggestions in the preparation of this report.

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BIOLOGY OF THE HUMAN VAGINA IN PREGNANCY*

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THE investigations of Hitschmann and Adler established the cyclical changes in the uterine endometrium and initiated a field of research which has yielded rich rewards. In the years that followed the observations of these authors numerous contributions have established the ovarian-uterine relationship. Attention has been focused on the kaleidoscopic changes in the uterine endometrium because of their magnitude and because menstruation, a signal event in the life of woman, heralds the termination of the cycle. It is only within recent years that the other derivatives of the müllerian system have been thoroughly investigated.

Wollner recently demonstrated cyclical changes in the cervical mucosa. The fallopian tubes and the vagina are likewise derivatives of the müllerian system. Seckinger and Snyder noted that spontaneous contractions of the fallopian tubes became more marked and rapid following ovulation and that this activity was greatly diminished during pregnancy. The recent work of Robert Meyer and Koff agreed on the fact that all of the vagina except the very distal portion is undoubtedly of müllerian origin. Thus the vaginal mucosa throughout most of its extent should be under the same influences as the uterine endometrium.

Study of the vaginal mucosa was given impetus by the work of Stockard and Papanicolaou who in 1917 introduced the vaginal smear method of following the sexual cycle in experimental animals. Daily vaginal smears in rodents give an accurate picture of the cyclical changes in these animals in that they reflect the changes in the vaginal mucosa. These basic experiments provided the test animals necessary for the rapid development of our knowledge concerning the endocrine glands associated with the sexual cycle.

The great difficulty in obtaining suitable human material and the absence of marked changes resulted in a variation of experimental results when the human mucosa was first studied. Thus Stieve in 1925 concluded that there were no regular cyclical changes in the human vagina in the nonpregnant individual. However, he described many changes during pregnancy resulting in a tremendous thickening of

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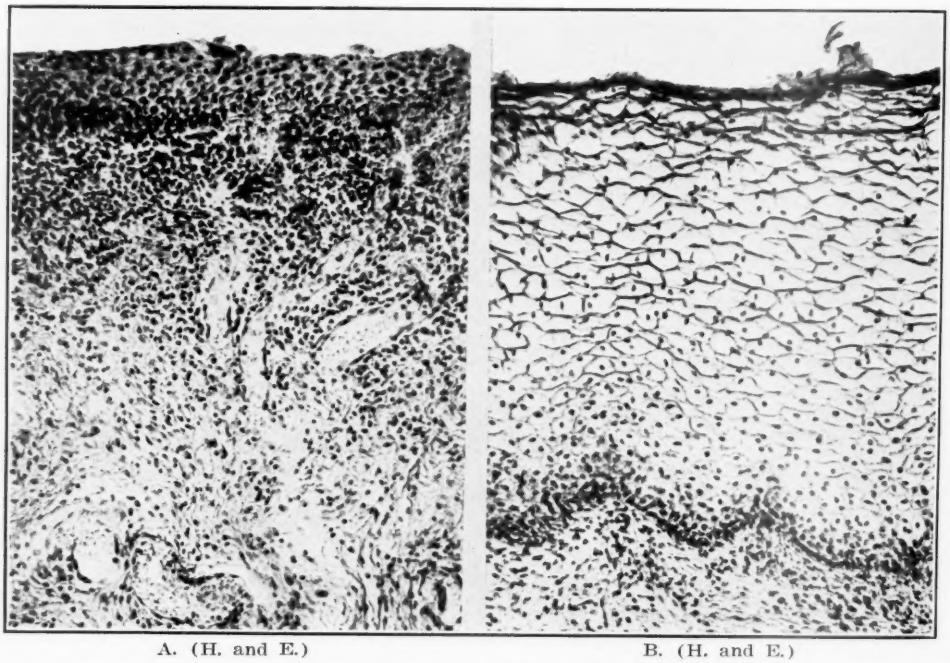
the vaginal mucosa. The loss of a good portion of this epithelium following parturition he ascribed to mechanical factors incident to delivery, such as stretching and trauma resulting in infection. As recently as 1936, Zondek and Friedmann questioned the ovarian control of the vaginal mucosa in the human in spite of the increasing amount of experimental evidence to confirm it.

Dierks and Puccioni in 1927 independently studied the vaginal mucosa in the human using suitable material and came to similar conclusions. They described characteristic histologic changes accurately correlated with the menstrual cycle. Their material was adequate and well controlled, thus establishing the existence of a vaginal cycle dependent on ovarian activity.



A. (H. and E.) B. (H. and E.)

Fig. 1.—H. and E. (160×.) (A) Biopsy from the vagina of a patient in the late postmenopausal period. The squamous epithelium is very low, consisting of four or five layers of cells. The individual cells are small, indistinct with opaque cytoplasm and dark staining nuclei. The basal layer of cells is irregular and devoid of a distinct basement membrane. There is a lack of cellular activity. (B) Biopsy from the vagina of the same patient taken after three weeks' treatment with estrogenic hormone. Note the marked proliferation of the squamous epithelium. The basal cells are regular, show marked activity. Most of the thickness of the epithelium is the result of many layers of large, discrete, vacuolated appearing cells. The uppermost layer or functionalis consists of desquamating, flattened cells. This is the characteristic histologic picture of a patient in the active sex years.

Davis and Hartman in 1935 carefully reviewed the work that preceded in an attempt to evaluate its significance. The primates are the only animals which menstruate. To determine the presence of a vaginal cycle in primates the authors began an investigation of a large series of monkeys in the Carnegie colony. Weekly biopsies of the vagina were made and the findings carefully correlated with vaginal smears and cyclical events in the ovaries. Their conclusions were that the vagina of the monkey undergoes cyclical changes perfectly coordinated with ovarian activity and ovulation. The next year Traut, Block and Kuder at Cornell University

confirmed these findings in the human species thus affirming the fact that in woman as in her near-kin, the higher apes, cyclical activity occurs in the vaginal epithelium.

Following up the experimental work on the monkey, Davis in 1935 reported an extensive study on the postmenopausal changes in the vaginal mucosa as a result of the normal or an artificial climacteric. He found that the squamous epithelium undergoes slow atrophy, the cells become smaller, the nuclei pyknotic. The basal layer of cells becomes inactive and loses its normal, smooth alignment on the basement membrane. The functionalis is lost and no cyclical activity can be seen. The thin, glistening, parchment-like mucosa, when subjected to even mild trauma, becomes damaged and if infection occurs it results in the clinical condition described as senile vaginitis. Upon the administration of estrogenic hormone in the form of suppositories or hypodermically, the senile vaginal mucosa undergoes a marked awakening. It becomes thicker, more velvety to the touch, pinker and now resembles the vagina of the young woman. Biopsies reveal a tremendous proliferation of the basal cells, the development of a thick basalis as well as a functionalis.

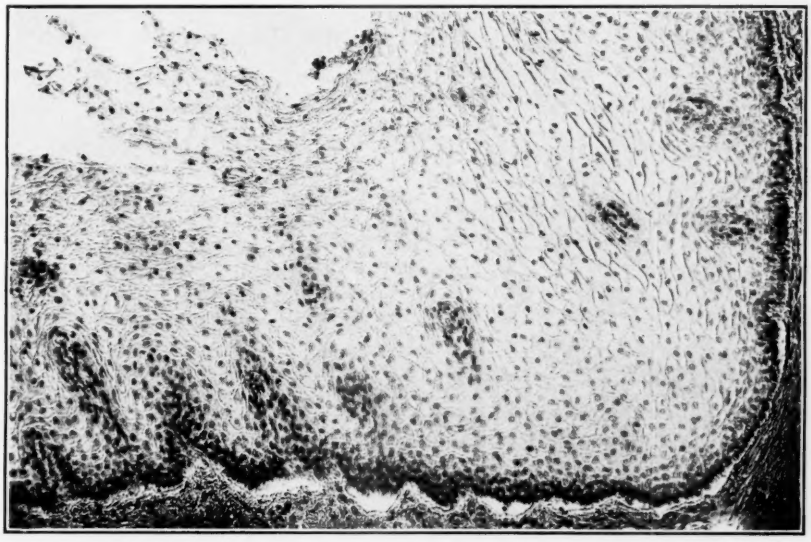
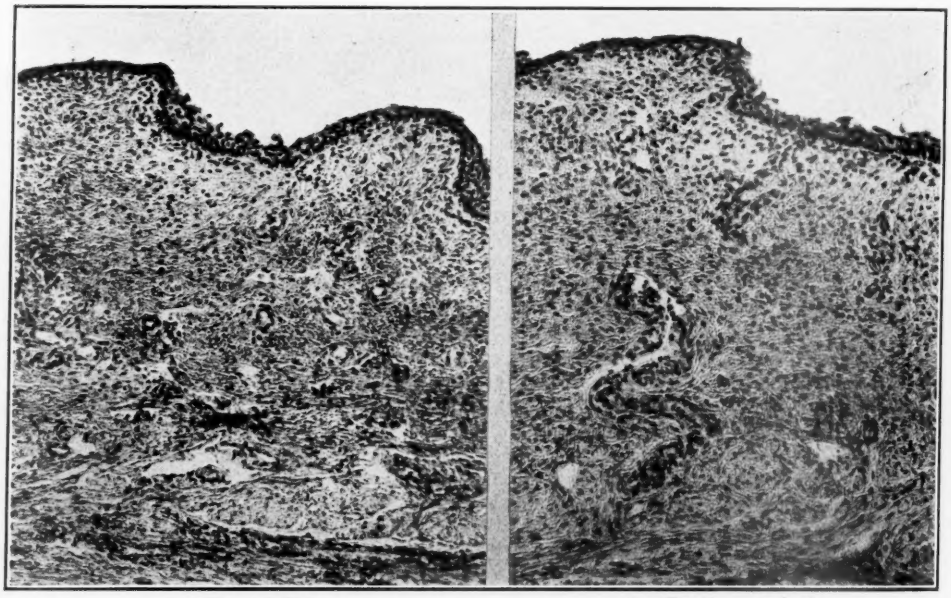


Fig. 2.—H. and E. (160×.) A section of the squamous epithelium of the vagina of a newborn baby. Note that it consists of many layers of large, clear cells with small nuclei. These cells are rich in glycogen. The basal cells are active consisting of several layers.

Microscopically, these changes are astounding as one can see from the photomicrographs (Fig. 1). These proliferative changes reach a maximum in ten days or two weeks and will remain thus as long as the estrogenic hormone is administered, but at its withdrawal retrogressive changes set in to continue until the vaginal mucosa has returned to its normal postmenopausal state. These experiments have resulted in a rational treatment for senile vaginitis which has stood the test of time.

Lewis, in 1933, following the experimental work of Corner and Allen on immature monkeys, described a treatment for gonorrheal vaginitis in children based on physiologic changes in the vagina which he had observed. The immature type of squamous epithelium of the vagina could be rapidly converted into the adult type by the use of estrogenic hormone. This adult type of vaginal epithelium with its abundance of glycogen usually results in the production of a marked vaginal acidity. This unfavorable reaction and the thickened adult type of epithelium are inimical to gonococci and they usually disappear.

Cruickshank and Sharman in 1934 reported careful studies on the histologic appearance of the vaginal mucosa in fetuses, infants, prepubertal and postpubertal children, and sex mature women. These can be briefly summarized. During intrauterine life, after the development of the epithelial covering of the vaginal lumen, it consists of twenty to thirty layers of large vacuolated cells with an active basal layer. In every way this epithelium resembles that seen during the active sex years (Fig. 2). Following delivery this epithelium becomes progressively thinner, the individual cells smaller, the basal cells less and less active. Within a month of extrauterine life the epithelium reaches its lowest ebb, consisting of several layers of small inactive cells (Fig. 3). This inactive epithelium remains unchanged during the developmental years of the growing girl until the onset of puberty and the initiation of hormone activity cause a rapid reawakening of the dormant epithelium. The mucosa becomes thicker, pinker, and more velvety to the touch. The basal layer of cells begins a rapid proliferation and the marked activity



A. (H. and E.) B. (Best's carmine)

Fig. 3.—(A) A section of the vaginal mucosa of an infant three months old. The squamous epithelium consists of three or four layers of small cells entirely inactive. This epithelium resembles that seen in the postmenopausal period. In both instances there is an absence of estrogenic hormone. (B) The same section stained for glycogen and showing its complete absence.

here is evidenced by the numerous mitoses. Twenty or thirty layers of cells are rapidly built up and the mucosa assumes the florid appearance of that of the mature woman, to remain thus until the cessation of ovarian function.

THE RÔLE OF GLYCOGEN IN THE VAGINAL EPITHELIUM

The presence of glycogen in the vaginal epithelium has been known for a long time. When present it is chiefly confined to the cells although the interstices also appear to contain it. Within the cell walls glycogen appears in the form of granules concentrated chiefly about the periphery of the cells. This granular form is not an artifact due

to tissue fixation for this characteristic distribution was retained when tissues were carefully fixed by the Altman freezing-drying technique of Gersh and Bensley, in which normal cell relationships are retained. The basal layers of actively proliferating cells contain no glycogen which is chiefly concentrated in the uppermost two-thirds of the epithelium. The large vacuolated cells which appear in hematoxylin-eosin stained sections contain the most abundant glycogen. As the cells reach the surface, become flattened and are about to be desquamated they still contain considerable glycogen.

The important rôle of glycogen in maintaining a normal vaginal acidity and a resultant normal flora was described by Krönig and Menge in 1897. These and subsequent workers realized that glycogen had to be converted into utilizable carbohydrates so that it could be attacked by vaginal bacteria and converted into lactic acid. Although the exact chemical process involved in this biologic mechanism is not definitely known, it is thought that glycogen is broken down by nonbacterial enzymes into a stage in which it can be attacked by bacteria. These organisms, largely Döderlein's bacilli, convert these utilizable sugars into lactic acid. These bacteria, because of their acid-resistance, are largely responsible for the high degree of acidity produced in the vagina which normally reaches pH 5.7 to 4.8 (Fig. 4). Possibly under certain circumstances Döderlein's bacillus can ferment glycogen directly into lactic acid.

Miura, in 1928, again drew attention to the presence of glycogen in the vagina, and from a large series of observations he concluded that there existed an intimate relation between the deposition of glycogen and ovarian activity as indicated by cyclical events, such as ovulation and menstruation. Cruickshank and Sharman in an extensive series of experiments and observations elucidated the facts concerning the biology of the vagina in the human subject. These workers corroborated many known facts and added new ones to explain the intricate mechanism present in the human to maintain normal biologic relationships.

The glycogen content of the vagina is dependent on the character of the epithelium which in turn is under the influence of estrogenic hormone, the result of ovarian activity. Thus the presence of glycogen has been demonstrated in the vagina of the fetus in the late prenatal period and in the newborn. The estrogenic stimulation to the vaginal epithelium probably is maternal in origin for within several weeks after birth the vaginal mucosa rapidly disintegrates resulting in an epithelium of several cells in thickness devoid of glycogen. This epithelium does not change throughout the developmental years of the girl until the onset of pubertal changes. The epithelium is built up to many layers of cells and an abundance of glycogen fills these cells. Soeken described abrupt changes in the vaginal acidity and flora associated with this change in the character of the epithelium of the vagina. These changes are brought on by the initiation of ovarian

activity and resultant cyclical changes. With the cessation of ovarian activity at the menopause, whether normal or artificially induced, the epithelium slowly reverts to six to ten layers of small, compact, rela-

Fig. 4.—This figure illustrates the dominant rôle of estrogen in the control of the biology of the vagina and of the character of its mucosa.

tively inactive cells, devoid of glycogen. Thus, the presence of glycogen in vaginal epithelium is dependent on an active, proliferating, many layered, sex-mature type of epithelium which in turn is dependent on estrogenic hormone (Figs. 5 and 6).

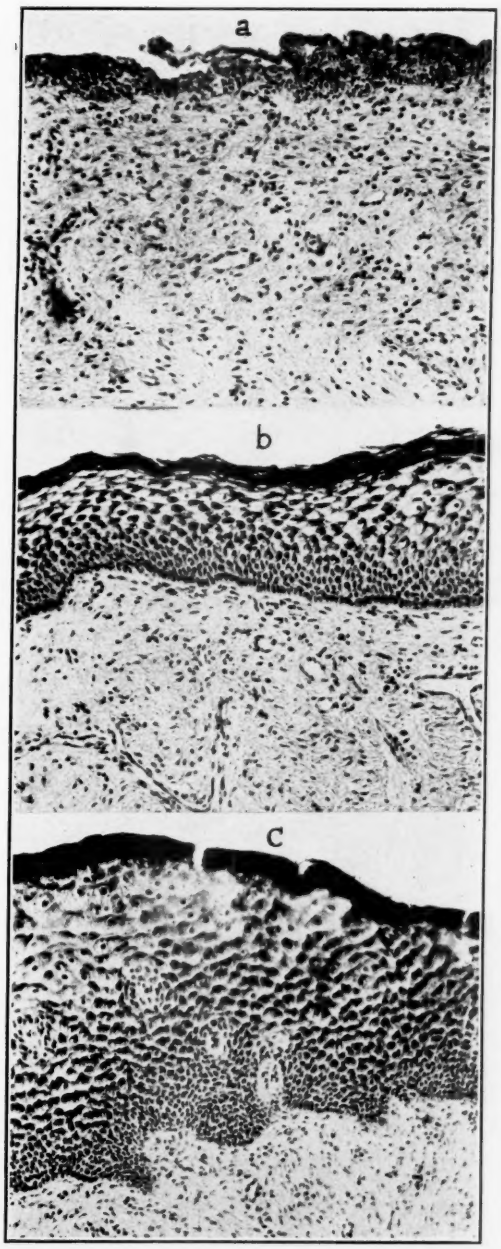


Fig. 5.—Sections stained with Best's carmine. (160×.) (A) Typical atrophic squamous epithelium of the postmenopausal period. (B and C) Two and four weeks following the administration of estrogenic hormone. Note the progressive increase in thickness of the epithelium and the marked deposition of glycogen in the vacuolated appearing cells. Note likewise the well developed functional layer which stains black as a result of the accumulation of glycogen in the flattened cornified cells of this layer.

PRESENT MATERIAL

This study was conducted along the same lines described in previous papers published by the author. Biopsies were obtained at two and three weekly intervals from the vaginas of a group of normal pregnant women throughout their pregnancies and for at least three months postpartum. Suitable biopsies can be readily obtained by means of a small punch previously described. As a rule a small amount of novocaine is infiltrated beneath the site to be biopsied, thereby raising the vaginal mucosa as a bleb, facilitating the removal of the biopsy specimen. There is little or no pain associated with this simple procedure even though no local anesthesia is used. Smears and cultures were taken prior to each biopsy removal.

The specimens were removed from the same portion of the vaginal wall so that comparative results would be more significant. The site

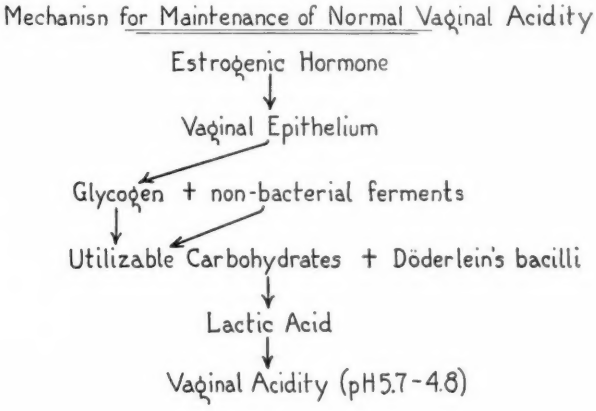

Mechanism for Maintenance of Normal Vaginal Acidity
Estrogenic Hormone
Vaginal Epithelium
Glycogen + non-bacterial ferments
Utilizable Carbohydrates + Döderlein's bacilli
Lactic Acid
Vaginal Acidity (pH 5.7 - 4.8)

Fig. 6.

selected was the lateral wall approximately six or seven centimeters from the introitus, in the upper third of the vagina. A previous study had demonstrated some slight variation of the thickness of the mucosa in the several parts of the vagina but these were of no appreciable significance. The tissue was immediately cut into two portions, one of which was fixed in absolute alcohol for glycogen studies, the other in Bouin's solution for histologic studies.

Gross changes in the vaginal mucosa became evident as the pregnancy advanced. The increasing vascularity occasionally resulted in some bleeding but this was easily controlled by a small tampon which was left in situ for several hours. A sharp punch will remove an uninjured piece of mucosa with its underlying tunica propria, thereby safeguarding normal relationships.

After fixation the specimens were carefully embedded in paraffin using a magnifying lens to assure a perfect lateral section. They were

cut about 5 microns in thickness and stained by hematoxylin and eosin. Special stains were used to study minute histologic features.

Best's carmine stain was used for the glycogen studies. This process stains the nuclei and cytoplasm of the cells a pale blue and the glycogen red. The efficacy of the stain and method was carefully controlled by using the method of Russell. He found that glycogen is dissolved by diastase in the saliva so that the former can be washed off in water whereupon when the section is stained by Best's method glycogen is absent in this control section. Some of the sections were counterstained by hematoxylin and eosin to accentuate the cytology.

We began our study on thirty normal women, the majority of which were primiparas. As the study progressed four of these women were dropped from observation due to premature termination of their pregnancies or to their failure to continue at the clinic. In two other women, regular biopsies could not be taken so that these were likewise discarded from this study. It was possible, therefore, to obtain regular biopsies during pregnancy, parturition and for three months postpartum on a group of 24 women (Table I). In a number of these women it was possible to obtain 15 biopsy specimens. These histologic studies were carefully correlated with studies of the cellular and bacteriologic content of the vaginal lumen. Papanicolaou has amply demonstrated that studies of the cellular content of the vaginal lumen in the human reflect accurately the changes taking place in the vaginal mucosa for the former is the result of the latter.

The deliveries of these women were accomplished in a number of ways. The majority delivered normally, the primiparas with the aid of an episiotomy. Some were delivered by the forceps operation. In two instances, fortunately for this study, elective cesarean section terminated the pregnancy. A number of possible candidates for this operation were purposely picked for the study. Stieve was so impressed by the traumatic factor in the postpartum changes in the vaginal mucosa that the elimination of all trauma of labor was desirable in a few cases in our series in order to evaluate their importance. One of our patients delivered twins near term. The reestablishment of menses in the postpartum period was noted in an attempt to correlate ovarian function and a return of cyclical changes in the vagina. Other than these facts, there was little in the clinical histories of the group of patients which would be pertinent to the present study.

PREGNANCY CHANGES

Davis and Hartman in 1935 reported the results of a study on the changes in the vaginal epithelium during pregnancy and the puerperium in a series of Rhesus monkeys of the Carnegie colony. These observations in many ways closely resemble the changes to be de-

TABLE I. VAGINAL BIOPSIES

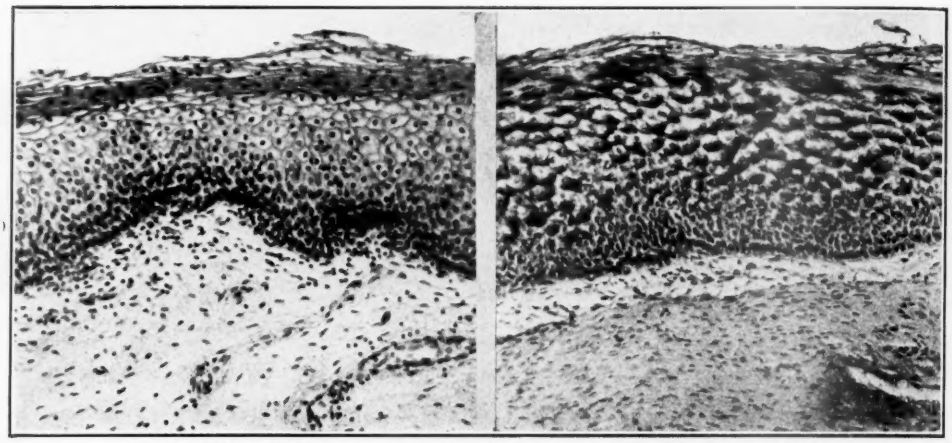
UNIT NO.	PARA	ANTEPARTUM										INTRAPARTUM	POSTPARTUM									
		WEEKS											DAYS				WEEKS					4 MO. AND OVER
		12	14	16	20	24	28	30	34	36	37, 38		1	6	8	9	4	6	8	9	10	
129781	i	+		+	+	+	+		+	+		+	+		+	+	+		+		+	+
128296	ii			+	+	+	+	+	+	+	+	+		+		+	+		+	+		
132516	i			+	+	+	+	+		+		+	+	+		+	+			+		+
133267	i	+	+	+	+	+	+	+	+	+	+	+			+		+		+			
131780	ii				+	+		+	+	+	+					+					+	
126760	ii			+	+	+	+	+	+	+	+	+				+						
133268	i				+	+	+	+	+	+	+	+	+	+			+		+		+	
126958	ii					+	+	+	+	+	+	+			+		+		+		+	+Menses
128643	iii				+	+	+	+	+	+					+		+				+	+
133263	i	+	+	+	+	+	+	+	+	+	+				+							
129741	i				+	+	+	+	+	+		+				+						
132063	ii		+	+	+	+	+	+	+	+	+	+				+						
133271	i			+	+	+	+	+	+	+		+	+	+	+	+		+				
129782	i		+	+	+	+	+	+	+	+	+	+			+							
133788	ii	+	+	+	+	+	+	+	+	+	+	+							+Menses+			+
134622	ii	+	+	+	+	+	+	+	+	+	+		+		+		+	+	+		+	+
132071	iii		+	+	+	+	+	+	+	+		+	+				+	+	+	+	+	+
99008	ii		+	+	+	+	+	+	+	+		+			+		+	+	+		+	
133791	iii	+	+	+	+	+	+	+	+	+	+	+					+	+				
133794	ii			+	+	+	+	+	+	+		+				+	+	+	+	+		+
131782	i		+	+	+	+		+		+				+				+				
133795	i				+	+	+	+	+	+	+	+	+		+				+			
76867	ii			+	+	+	+	+	+	+		+			+							
133269	i				+	+	+	+	+	+		+	+			+			+		–	

scribed in the human female. This is not a surprising fact for this experimental animal and the human female are the only primates who exhibit cyclical and endometrial changes eventuating in menstruation. Furthermore, these primates are the only species in which glycogen is present in the vagina. Thus, it would appear that the physiologic changes in the genital tract should be analogous.

The vaginal epithelium as early as the twelfth week of gestation shows marked thickening, reaching a thickness of 500 microns near the end of gestation. An active proliferation of the basal cells can be seen, and four or five layers of actively dividing cells constitute the basal portion of the epithelium. Numerous mitotic figures bear evi-

Fig. 7.—This is a high power of the superficial portion of the functional layer showing the desquamation of the cells. Note how they literally crumble away from the surface. These cells, although distinctly necrotic, still contain an abundance of glycogen.

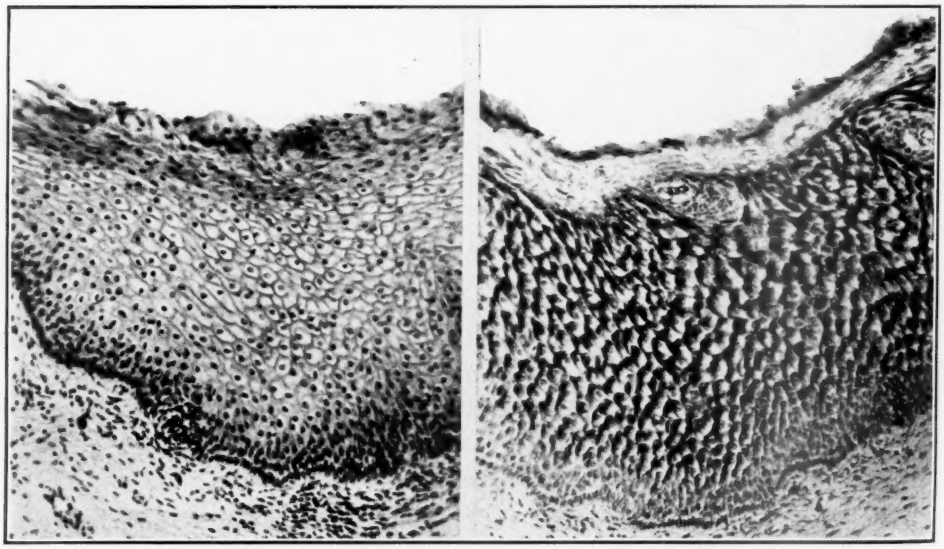
dence of this active cell division. Above these actively proliferating cells one can count 20 to 30 layers of large vacuolated-appearing cells in which the nuclei stand out prominently. These cells are normally laden with glycogen and the vacuolization is in part the result of a disappearance of glycogen in the fixation of the tissue. The uppermost layer or functionalis consists of cells from the lower layers which have worked upward. They have become flattened and compressed but still contain an abundance of glycogen in their cytoplasm. The superficial cells of this layer are continually breaking away from their attachment (Fig. 7). This extensive desquamation provides the profuse



A. (H. and E.) B. (Best's carmine)

Fig. 8.—This is the first of a series of five sections taken during various periods of pregnancy and stained with hematoxylin-eosin and Best's carmine for glycogen. They are all of the same magnification (160×) and therefore provide a good comparison as to the thickness of the epithelium and the changes in its cellular structure.

Biopsies taken at eleven weeks' gestation. (A) This section shows the epithelium of moderate thickness. The basal layer consists of three or four layers of cells in which there are signs of cellular activity. The functional layer stands out distinctly. (B) In this glycogen preparation one can note that the middle layers of cells which appear in the previous section as vacuolated contain an abundance of glycogen. There is, however, an absence of glycogen in the three or four layers of active basal cells. The functionalis likewise contains considerable glycogen.



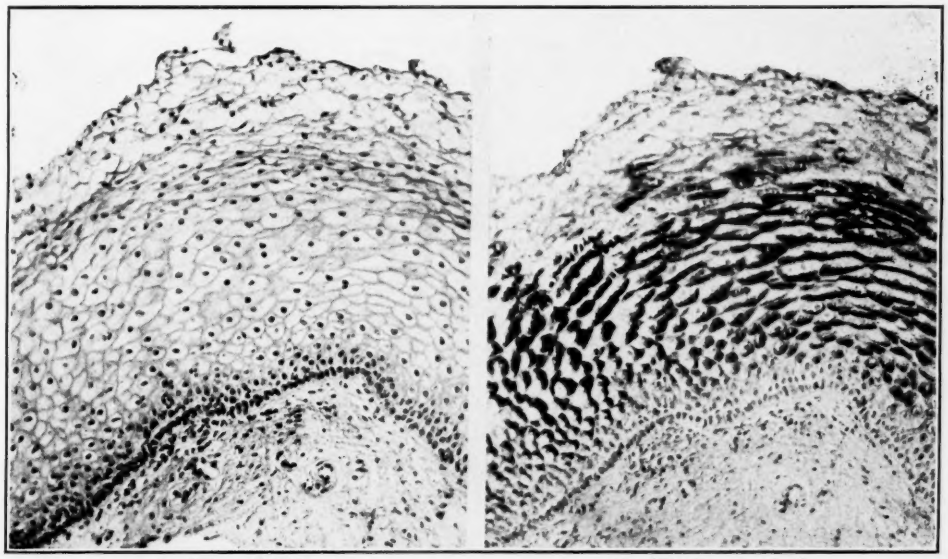
A. (H. and E.) B. (Best's carmine)

Fig. 9.—Biopsies taken at fourteen weeks' gestation. (A) This section shows the progressive increase in the thickness of the epithelium as well as in the activity of the basal cells. (B) The glycogen can be seen in these cells in the form of granules surrounding the nucleus.

characteristic secretion in the vaginal lumen as well as the glycogen necessary for the maintenance of the vaginal acidity (Figs. 8 through 12).

In the functionalis one can see large abnormal appearing cells, some round or oval, others oyster-shaped with large round nuclei. These cells probably represent the so-called "pregnancy cells" which Papanicolaou has described in the cellular content of the vaginal lumen during pregnancy.

The maximum proliferation and development of the vaginal mucosa is probably reached at mid pregnancy and this condition is maintained until near the end of gestation. There is some variation in different



A. (H. and E.) B. (Best's carmine)

Fig. 10.—Biopsies taken at twenty-two weeks' gestation. (A) Except for the increase in the thickness of the epithelium there is little change from the previous section. (B) Histologically there appears to be a distinct increase in the amount of glycogen in the individual cells. Note likewise the increased thickness of the desquamating layer.

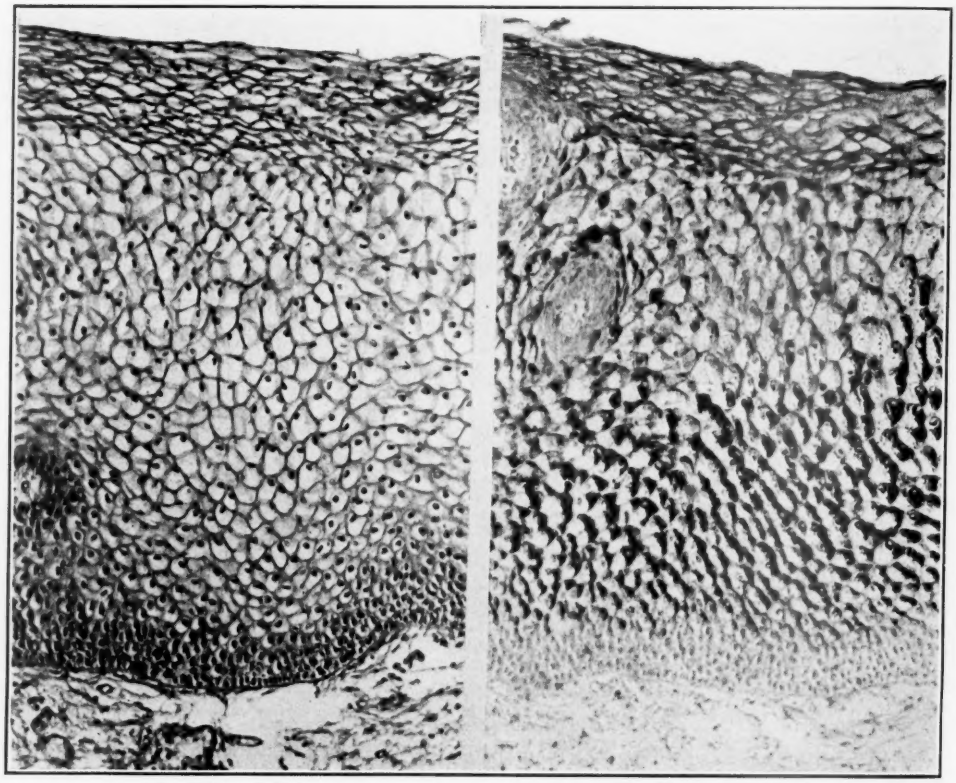
individuals so that the cellular development is greater in some than in others. However, one can follow the changes described in all the normal gestations.

As term approaches one notes a diminution in the thickness of the vaginal epithelium in a majority of the patients. This is not as marked as in the case of the monkey but nevertheless the change in the epithelium is sufficient to be noted. The cells still contain an abundance of glycogen but there is considerably less activity in the basal cells than was evident in early gestation.

The profuse, creamy, whitish secretion of normal pregnancy consists largely of desquamated epithelial cells, cervical mucus and Döderlein's

bacilli. The amount of this secretion increases as pregnancy advances. This increased amount is largely due to the cytologic activity of the vaginal epithelium. The reaction is acid and Miura has estimated that the amount of titrable lactic acid increases from 0.4 per cent early in pregnancy to 0.9 per cent by the end of pregnancy.

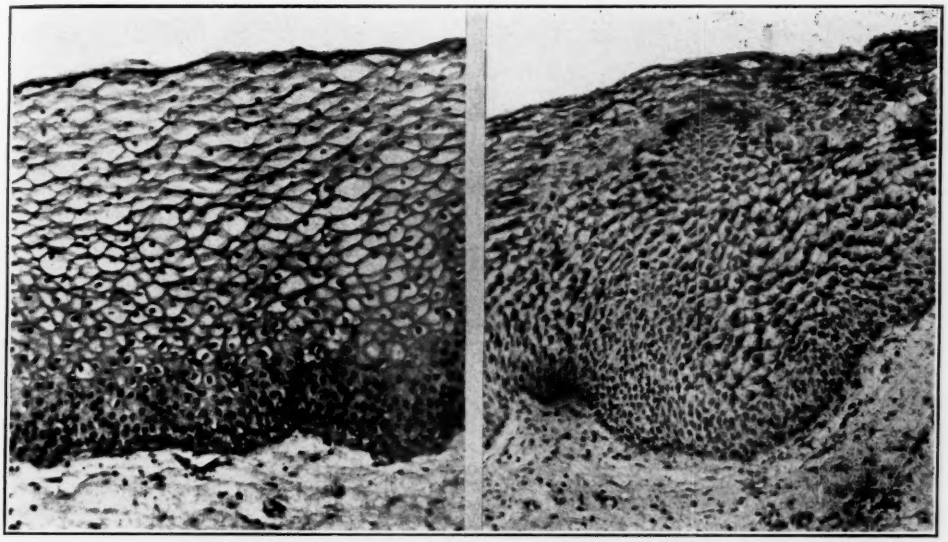
Following the birth of the baby marked retrogressive changes rapidly manifest themselves in the vaginal mucosa. It becomes progressively thinner so that at the end of two weeks the entire thickness



A. (H. and E.) B. (Best's carmine)

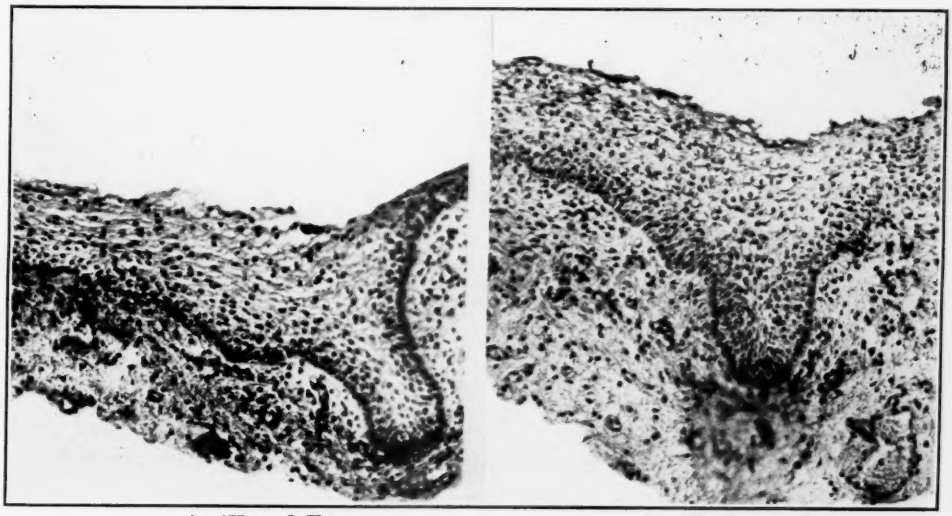
Fig. 11.—Biopsies taken at thirty-six weeks' gestation. (A) The thickness of the epithelium has apparently reached the maximum although there seems to be less activity in the basal layer of cells. Note particularly the rather marked differentiation of the epithelium into its various component parts. (B) The distribution and character of the glycogen in the large vacuolated cells is particularly well demonstrated in this section.

may comprise six to ten layers of cells. The basal cells consist of a single layer of small cells, somewhat irregularly arranged on the basement membrane. The normal orderly alignment of discrete cuboidal cells on a clean cut basement membrane present prior to delivery is missing. The individual cells are small, with dark nuclei and show no evidences of cellular activity. The remaining cells likewise have become smaller, more compressed and irregularly arranged. Gone are



A. (H. and E.) B. (Best's carmine)

Fig. 12.—Biopsies taken at thirty-eight weeks' gestation. (A) At term there appears to be a decrease in the thickness of the epithelium as well as a diminution in its activity. This is not a consistent finding but it is very common. (B) There likewise appears to be a diminution in the amount of glycogen present at this period of the gestation.



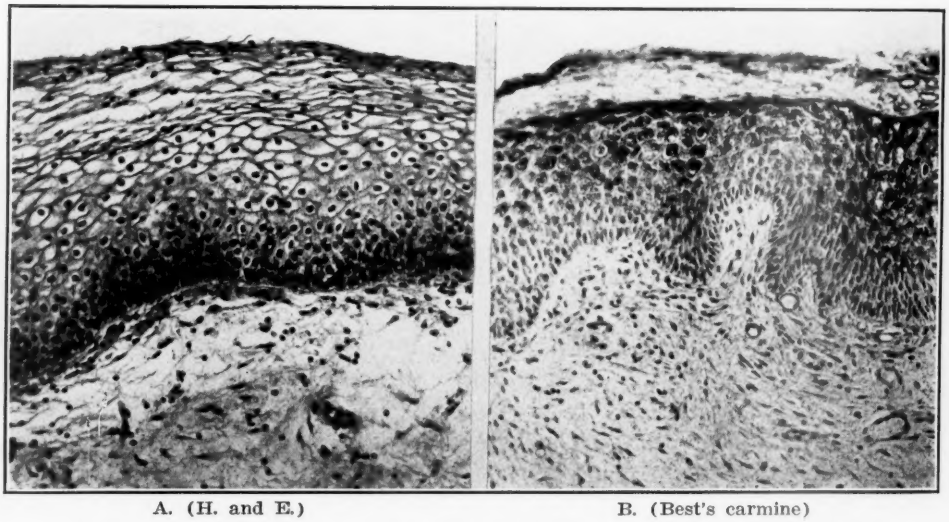
A. (H. and E.) B. (Best's carmine)

Fig. 13.—This is the first of a series of three sections taken during the postpartum period in the same patient. They are all of the same magnification (160×) and therefore provide a good comparison as to the thickness of the epithelium and the changes in its cellular structure.

Biopsies taken at eight days postpartum. (A) Note the marked decrease in the thickness of the squamous epithelium. A large portion of it has been lost by desquamation. The individual cells are small and appear distinctly inactive. The large vacuolated cells of the pregnancy period have disappeared. (B) This section stained for glycogen shows its total absence.

the large, clear cells which formerly were filled with glycogen and the functionalis with the desquamating epithelial cells. In fact the epithelium has reverted to the type almost characteristic in the postmenopausal period, inactive and devoid of glycogen (Fig. 13).

The extent of the destructive processes described varies considerably in different individuals but the general picture is present in all. The absence of glycogen in the cells is particularly significant. That these changes are not the result of changes incident to the trauma of labor itself is evident from the fact that the type of delivery does not affect the subsequent changes in the vaginal mucosa. The patients delivered by cesarean section where no vaginal trauma has taken place exhibit similar changes.



A. (H. and E.) B. (Best's carmine)

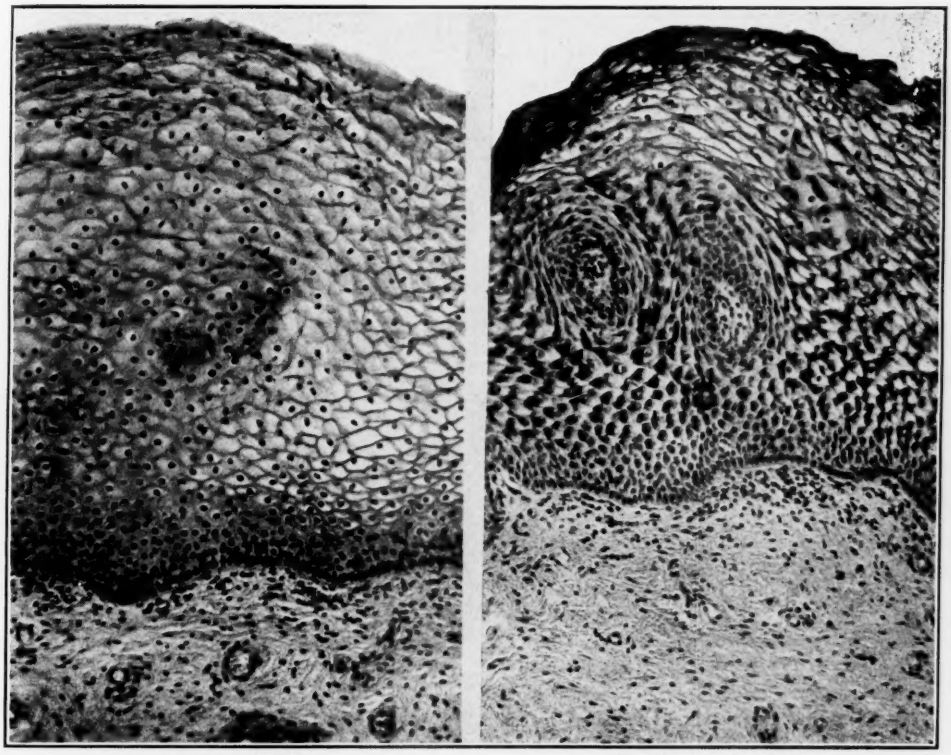
Fig. 14.—Biopsies taken at five weeks postpartum. (A) The squamous epithelium is again proliferating. This is best seen in the basal layer which consists of three or four layers of active cells. A functional layer is likewise developing. (B) In the glycogen preparation one notes particularly the recurrence of glycogen in the vacuolated cells as well as in the desquamating cells of the functionalis.

Unfortunately, the vaginal secretion and possible changes in the vaginal flora cannot be studied during the puerperium for lochial discharges resulting from uterine involution completely obscure any vaginal findings.

Four to six weeks postpartum the epithelium begins to show signs of proliferative activity (Figs. 14 and 15). This is first apparent in the basal layers of cells in which cell division and growth are manifest. Soon three or four layers of cells comprise this layer. These cells are packed close together. They contain little cytoplasm and their nuclei stain darkly and contain numerous mitoses. The epithelium grows in thickness by a rapid increase of large, vacuolated appearing cells

which are filled with glycogen. Finally, the functionalis appears and the flattened, nonnucleated, glycogen containing cells begin to crumble away from the surface of this layer. Usually the vaginal mucosa is completely restored within six or eight weeks following childbirth. The recurrence of the menses is usually indicative of renewed cyclical activity although the vaginal mucosa is most often completely restored before the menses are reestablished.

Following gestation there is an immediate and rapid drop in the estrogenic level in the blood and urine of the patient. This results in



A. (H. and E.) B. (Best's carmine)

Fig. 15.—Biopsies taken at nine weeks postpartum. (A) The vaginal mucosa has not completely recovered following the reestablishment of cyclical activity in the ovary. (B) Note the characteristic glycogen distribution is once again manifest.

a rapid retrogression on the part of the vaginal epithelium. It becomes thinner, the cells smaller and inactive. Glycogen entirely disappears from the cells. Undoubtedly the vaginal secretion changes and the acidity disappears but these changes are masked by the profuse bloody uterine discharge. The epithelium remains in this inactive state until the initiation of follicle activity in the ovary results in a reestablishment of cyclical activity in the genital tract.

The changes in the vaginal mucosa that result from pregnancy and parturition are entirely under estrogenic control. These observations

confirm the rôle of estrin in the maintenance of biologic relationships in the vagina. During pregnancy there is present an excessive production of this hormone and a marked increased concentration in the blood. Just where it is produced is still questionable. Under the influence of this abundant hormone, the vaginal mucosa undergoes its most marked proliferation. The cells become large and filled with glycogen. The increased activity on the part of the epithelium results in an excessive desquamation of cells from the thickened functionalis. These desquamating cells, rich in glycogen, result in a profuse characteristic, highly acid, vaginal secretion. Döderlein's bacilli in almost a pure culture provide the ideal flora necessary to maintain this vaginal acidity or thrive because of it.

DISCUSSION

The intricate mechanism for the control of biologic relationships in the vaginal tract is the result of morphologic changes in the vaginal epithelium, chemical changes and bacterial flora. Thus, the flora is dependent on the vaginal acidity, the vaginal acidity is the result of the action of enzymes on the glycogen, and the presence of glycogen is dependent on an actively proliferating epithelium. The latter is under the influence of estrin. These factors are therefore all under ovarian control. During pregnancy and parturition these are still under estrogenic control although the source of this hormone is not definitely known. Disturbances of any of them may easily upset the delicate balance, resulting in pathologic consequences.

These basic facts just described provide a logical explanation of the causation and therapy of many clinical conditions. Suffice it here to touch on a few of these. Yeast vaginitis is a particularly troublesome infection of the lower genital tract that occurs most often during pregnancy. It is almost impossible to eradicate this condition during pregnancy and the symptoms are difficult to control. Following parturition the infection disappears without treatment, occasionally to recur at a later date. Pregnancy provides an ideal opportunity for a yeast infection of the vagina, for the abundance of glycogen in the vaginal mucosa results in an ample supply of utilizable sugars and an acid medium. Both of these factors are necessary for the growth of yeast cells, so that if these organisms are present in or are introduced into the vagina, pregnancy offers the ideal conditions for their growth. Following delivery, the retrogression of the vaginal epithelium and the disappearance of glycogen remove the necessary factors so that the fungi quickly disappear and the patient is cured of her vaginitis.

The author has seen three cases of gonorrheal infection in the lower genital tract in the late postmenopausal period. The infection here

as in childhood selects as the site of predilection the vaginal mucosa. The atrophic, senile vaginal epithelium is no defense against the gonococcal penetration and the absence of glycogen with the resultant alkaline reaction of the scant secretion offers a favorable medium for these organisms. The resulting infection is predominantly a vaginitis. The only treatment used was estrogenic hormone in the form of vaginal suppositories, and the rapidity of disappearance of symptoms and organisms was astounding. Within ten days these patients were symptom-free and had negative smears. The senile, atrophic mucosa was replaced by an active, proliferating epithelium of the sex-mature type.

The rational treatment of senile vaginitis and gonorrheal vaginitis in children has been previously alluded to. These examples should lead to continued advances in rationalizing the treatment of lower genital tract infections.

Papanicolaou in 1933 suggested that smears of the cellular contents of the human vaginal lumen would reveal the character of the cyclical changes in the ovary. Furthermore, pregnancy resulted in a typical vaginal smear of considerable diagnostic importance. Smith and Brunner have just published the results of their study on the use of vaginal biopsies in the diagnosis of pregnancy. Papanicolaou and Shorr recently demonstrated the value of the vaginal smear as an index of the action of ovarian follicular hormone in the therapy of the menopause and endocrine disturbances.

Lastly, the intricate biologic mechanism for the control of vaginal acidity must have many important functions. Certainly it is not bold to imagine that one of these functions is to guard against infection of the genital tract during pregnancy, labor and the puerperium. The rapid changes that take place following delivery may lead to pathologic consequences. Perhaps additional safeguards can be found to maintain the elaborate set-up already present in a high degree of efficiency, thereby minimizing undesirable sequelae.

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DISCUSSION

DR. GEORGE W. BARTELMEZ.—The relationship between activity in the vaginal epithelium and the concentration of estrogenic hormone seems to be very definite. Yet it is well to remember that the endocrines associated with the female reproductive system represent a very delicately balanced mechanism. The introduction of any hormone involves a change in the organism as a whole. It is possible that estrin does nothing more than increase the circulation in the reproductive tract and as a result we get greater mitotic or secretory activity. On the other hand, it may be that other hormones are also involved. At the present time it looks as if in the absence of the anterior lobe of the hypophysis all the characteristic effects of estrin can be obtained. No one has as yet removed all the other endocrines from an animal and then used estrin.

I should like to ask Dr. Davis whether he has seen any evidence of reduction in the activity of the vaginal epithelium weeks or months before the end of pregnancy. There are not a few instances in which it looks as though the ovary had become quite inactive long before the end of pregnancy. Stieve has described two cases in which he could find no evidence of a corpus luteum in either ovary during the last third of pregnancy. It would be interesting to know whether in such instances there was evidence of regression in the vaginal epithelium, even though plenty of estrin is being produced in the placenta.

DR. ARTHUR KOFF.—The recent work by Meyer and others seems to show that the vagina has a double origin. Certainly most of the upper part of the vagina is derived from the müllerian system, and some portion of the lower third, just how much it is impossible to say, is derived from the urogenital system.

It is important to take biopsies in work such as this from the upper third of the vagina, for that portion which is derived from the urogenital system may not take part in the cyclic changes of the rest of the genital tract.

DR. ROBERT M. GRIER.—I would like to ask Dr. Davis whether there were any special changes noted in those mothers who were nursing babies. Many nursing mothers do not menstruate. It has been assumed they do not ovulate.

If this is true, then there should be no ripening follicles to produce estrin and the vaginal epithelium should show the absence of this hormone in the lack of full development of a squamous layer much as is seen before puberty and after the menopause.

DR. DAVIS (closing).—In a number of our cases we noted a decrease in the thickening of the squamous epithelium and likewise a decrease in glycogen a week or ten days before the onset of labor. That did not occur in all cases. What we presented here was a typical case, one of twenty or twenty-one typical cases. Whether this decrease of the activity of the squamous epithelium is due to decrease in estrogenic hormone we cannot say. We have as yet had too few good curves of estrogenic hormone during pregnancy and after delivery.

All our biopsies were taken in the upper third of the vagina. I agree it is important to take all the biopsies from the part of the vagina that we know definitely is of müllerian origin.

We did not correlate our study with nursing. It is certainly an interesting point to note whether nursing mothers do get changes in the squamous epithelium during the postpartum period. We did attempt to correlate the vaginal changes with the recurrence of the menses to see whether normal cyclical activity occurred before or after the onset of menses.

Bland, Brooke and Rakoff, A. E.: The Incidence of Trichomonads in the Vagina, Mouth and Rectum, J. A. M. A. 108: 2013, 1937.

This study of the incidence of trichomonas from the vagina, mouth, and rectum of 200 women employed wet smears, stained slides and culture methods. Vaginal infestation with trichomonas was common, occurring in 23 per cent of the group. Buccal infestation occurred in 16.5 per cent of the patients, while intestinal trichomonas was comparatively rare, being present only in 1.5 per cent of the women.

It was demonstrated that the wet smear method is the most efficient for the diagnosis of *Trichomonas vaginalis,* while the culture method was more superior for the detection of the intestinal and buccal trichomonads. Women harboring vaginal trichomonas did not show an appreciable higher percentage of buccal or intestinal trichomonads than were noted for the group at large. Only one woman harbored all three organisms.

Rectal contamination was regarded as an improbable source of vaginal infestation in view of the rarity of intestinal trichomonas among women with *Trichomonas vaginitis.* Of three patients harboring intestinal trichomonads, only one was positive for *Trichomonas vaginalis* despite the fact that the flagellates could be regularly demonstrated in the feces over long periods of time. Autoinfestation with buccal trichomonads was also considered an unlikely source of vaginal infestation because the dual incidence of these organisms was not more than would be expected from chance distribution. A comparison of the incidence of trichomonads from the bowel and mouth indicates that intestinal infestation probably does not result from ingestion of the buccal forms.

Unlike the intestinal and buccal trichomonads, *Trichomonas vaginalis* was not cultivable at room temperature and was considered physiologically different.

GROVER LIESE.

IDENTIFICATION OF YEASTLIKE ORGANISMS ISOLATED FROM THE VAGINAL TRACTS OF PREGNANT AND NONPREGNANT WOMEN

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(From the Department of Obstetrics and Gynecology and the Department of Bacteriology, Duke University Medical School)

YEASTLIKE organisms have been cultured frequently from the external genitalia and vaginal tracts of women suffering from vulvovaginitis. Proof of the etiologic relationship of these fungi to mycotic vulvovaginitis is complicated by the fact that yeasts also occur in a significant percentage of women who show no signs or symptoms of vulval or vaginal irritation. Attempts to correlate the presence of these fungi with the clinical findings are handicapped by the lack of practical methods for identifying yeastlike organisms.

Castellani's[1] classification which is based on the ability of the organism to ferment certain carbohydrates has not been found practical. Benham[2] accomplished much in the way of correlating the morphologic, biologic and serologic characteristics of the yeastlike fungi but her methods of identification are too complicated for routine use. The identification key proposed by Stovall and Bubolz[3] is much simpler in technique but others[4, 5] have found strains which cannot be classified in one of the three types proposed by these authors.

Our study describes the methods developed for the identification of 68 strains of yeastlike fungi isolated from the vaginal tracts of pregnant and nonpregnant women. These fungi were isolated during a routine study of the complete vaginal flora by Carter and Jones,[6] and no correlation with the clinical findings was attempted. Representative strains were obtained from Drs. Benham and Stovall, and a comparison of our technique with the methods described by these authors was thus possible. We present only the details of the procedures necessary for identification. A review of the literature with a more complete discussion of terminology and methods of classification is to be published elsewhere.

MATERIALS AND METHODS

Sixty-eight strains of yeastlike fungi were isolated from the vaginas of 52 pregnant and 16 nonpregnant women. In a nonpregnant patient a sterile speculum was inserted and the swab smeared over the posterior fornices of the vagina. Care was take not to touch the speculum with the swab. In a pregnant woman no speculum was used; the labia were spread by an assistant and the swab was inserted directly into the vagina. All swabs were streaked on Sabouraud's slants and were smeared

on glass slides for direct examination. Budding yeast cells were seen in these smears in a high percentage of those cases in which cultures were subsequently positive. The cultures were incubated at room temperature. Since bacteria frequently develop on Sabouraud's medium, fungi when found were checked for purity by inoculating Sabouraud's acid dextrose broth and streaking a blood agar plate from this broth culture. We believe that some of the irregularities of carbohydrate fermentation noted by other observers may be due to the presence of two or more species of fungus on the original Sabouraud's slants or to an occasional bacterial contaminant. Blood agar, although not an ideal medium for the development of yeastlike fungi, is a very useful substratum for colony differentiation.

The following technique which was developed by empirical methods enabled us to identify all 68 strains studied. The procedures necessary for identification were:

1. Colonies on Sabouraud's dextrose agar were transplanted to Sabouraud's acid dextrose broth, incubated at 37° C. for forty-eight hours and the type of surface growth noted.

2. A beef extract blood agar plate, pH 7.4, was streaked from this Sabouraud's broth culture after shaking the tube to resuspend the sedimented organisms. These plates were incubated at 37° C. for ten days. Although most colonies developed well in three or four days certain types of monilia showed typical colonies only after longer incubation. If bacterial colonies appeared or two species of fungi were recognized, a single colony was selected and inoculated into another tube of Sabouraud's broth to observe the type of surface growth of the pure culture.

3. A single well isolated colony was picked from the blood agar plate and planted on a second Sabouraud's dextrose agar slant. After incubation either at room temperature or 37° C. some of the growth was transplanted to a sterile carrot plug which was subsequently examined at frequent intervals for evidence of ascus formation.

4. A beef extract dextrose-free agar slant was inoculated from the Sabouraud's agar slant which was used as inoculum for the carrot plug. This culture was incubated at 37° C. for twenty-four hours and subcultured 2 or 3 times. The most recent transplant was used to inoculate the various carbohydrate broths, milk, and corn meal agar slide cultures.

5. The carbohydrate fermentation reactions were tested by inoculation of beef extract broth containing 1 per cent of fermentable substance. Beef extract broth containing brom-thymol-blue was titered to pH 7.2 before autoclaving at 15 pounds' pressure for twenty minutes. After cooling, the carbohydrate solutions, sterilized by filtration, were added. The inoculum consisted of a saline suspension of the scanty growth on beef extract agar. The growth was washed off in 1.0 c.c. saline and 0.1 c.c. quantities were pipetted into the various carbohydrate broths and milk.

6. Corn meal agar was prepared as described by Benham[2] and a slide culture made by flooding a sterile slide with the molten medium. After hardening, the agar was inoculated by making a heavy streak the length of the slide, splitting the medium. The inoculum always consisted of material from the beef extract agar slant. The slides were incubated at room temperature for several days in sterile moist chambers. After mycelial growth had occurred the slide was dried in the air, and fixed and stained with lactophenol and cotton blue.

7. Agglutination tests with immune rabbit serums were done with most strains.

None of the 68 strains produced asci on carrot plug and 9 failed to develop mycelia on corn meal agar. These 9 strains were classified as cryptococci and corresponded to Group I as described by Benham.[7] The remaining 59 strains, which produced mycelia, were considered species of the genus *monilia* as this genus is generally interpreted in medical literature: i.e., yeastlike cells which reproduce by

budding and by the formation of a mycelium, but which do not produce asci or aerial hyphae. Although the name *monilia* is invalid according to rules of botanical nomenclature, we have retained it in order to avoid the confusion that invariably follows changes in terminology. We have adopted the same species terminology as was used by Benham.[2]

The strains isolated from the vaginal tracts were identified as follows:

Monilia albicans	19 strains
Monilia parapsilosis	3 strains
Monilia candida	4 strains
Monilia Krusei	4 strains
Monilia stellatoidea n. sp.	29 strains
Cryptococcus sp.	9 strains

Fig. 1.—Colonies of *M. albicans* on beef extract blood agar pH 7.4, incubated at 37° C. for ten days.

CULTURAL CHARACTERISTICS

It should be emphasized that only gross differences in the type of growth in the various substrata are presented; minor variations not essential for identification are omitted. For example, the most obvious difference between *M. Krusei* and the other species of monilia on Sabouraud's dextrose agar is the flat dry growth of *M. Krusei* as compared with the moist creamy growth of the other species.

Growth in Sabouraud's Broth (48 Hours at 37° C.).—All species produced in this medium a growth which settled to the bottom of the tube leaving the supernatant

fluid relatively clear. *M. Krusei* and *M. candida* were the only species which produced any growth on the surface of the medium within forty-eight hours. All strains of *M. Krusei* produced a dry thin "collarlike" growth which extended up the sides of the tube to a distance of 5 or 6 mm. above the surface of the medium. Surface growth occurred with all strains of *M. candida* but the "collar" was narrower (2 or 3 mm.) and the surface film tended to be broken up by small bubbles of gas. Strains of other species occasionally produced surface growth irregularly if the tubes were incubated longer than forty-eight hours.

Colony Formation on Blood Agar (10 Days at 37° C.).—Characteristic colonies were obtained only if the blood agar plates were inoculated from Sabouraud's broth cultures. If subcultured from Sabouraud's dextrose agar or from beef extract agar, growth may or may not be typical.

Fig. 2.—Colonies of *M. stellatoidea* on beef extract blood agar pH 7.4, incubated at 37° C. for ten days.

M. albicans: Well isolated colonies were circular, approximately 1.5 mm. in diameter and the borders were smooth and regular. The surfaces were slightly convex and appeared dull grayish white (Fig. 1).

M. parapsilosis: These colonies were uniformly smaller than those of *M. albicans* (0.6 to 0.8 mm. in diameter) and more convex. The color was a definitely pearly white.

M. candida: This species produced the largest colonies on blood agar, attaining sizes of 2 mm. and more. The most characteristic feature was the wide "mycelial fringe" surrounding the colony. The mycelia grew only beneath the surface of the medium and formed a peripheral zone about 1 mm. wide around the entire colony. These colonies were grayish white in color but not as dull as the colonies of *M. albicans.*

M. Krusei: The growth of these organisms was characterized by the irregularity in size and shape of colonies which appeared to be equally well isolated. There were variations in size (0.2 to 1.0 mm. in diameter), the surface appeared flat, ridged or nodular, and the edges of different colonies were smooth and round or coarsely irregular.

M. stellatoidea: This organism, which resembled *M. albicans* very closely on Sabouraud's dextrose agar, presented a very characteristic appearance on blood agar. The surface was heaped up in the center and from this center zone "arms" radiated in an irregular fashion. These projections were thick near the center and narrowed at the periphery, giving the colony an appearance not unlike that of a "star in the sky" with its surrounding radiations of light (Fig. 2).

Cryptococcus sp.: All strains of this fungus grew very poorly on blood agar and never attained any appreciable size.

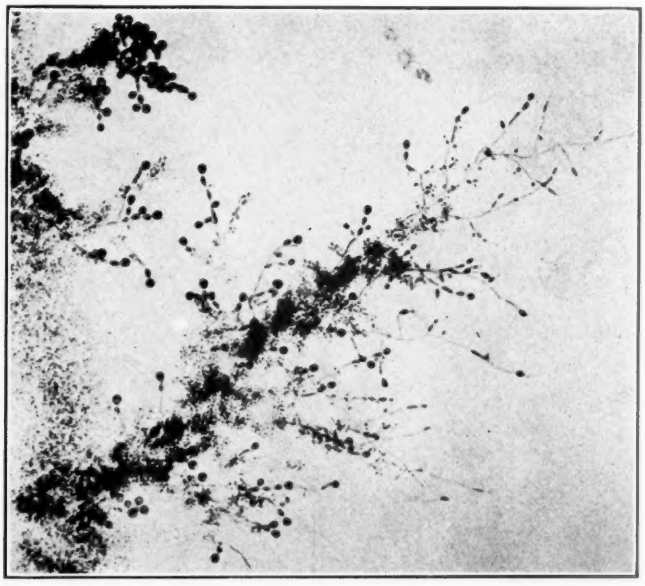

Fig. 3.—Photomicrograph of corn meal agar slide culture of *M. albicans* fixed and stained with lactophenol cotton blue.

Mycelial Development on Corn Meal Agar (Several Days at Room Temperature).—Constant results on this medium were obtained only if the inoculum had been on the sugar free medium (beef extract agar) for several generations. Different strains of the same species showed variations in mycelial development but certain "typical" structures were usually present. The following descriptions are confined to the most constant features found in each species.

Monilia albicans usually produced a well-developed branched "tree-like" mycelium which did or did not extend far from the original streak. The most constant finding was the development of numerous swollen double contoured cells (chlamydospores) on the tips of most all branches (Fig. 3).

M. parapsilosis: The mycelium seemed to form much less readily than in any other species, but after development occurred branching was profuse. There were no chlamydospores.

M. candida: The mycelium developed readily and extended far from the line of streak. The main mycelial threads grew in straight parallel rows and the lateral branches were shorter than those of *M. albicans.* There were no chlamydospores.

M. Krusei produced mycelia which, when well developed, showed long branches occurring at rare intervals. Clusters of long thin spores were found arranged like a bundle of crossed sticks.

M. stellatoidea formed mycelia readily and was characterized by large numbers of large balllike clusters. These developed on the mycelial strands and grew so closely together that the mycelial threads connecting the clusters were difficult to see. A single chlamydospore was found in 2 of the 29 strains studied (Fig. 4).

Cryptococcus sp.: No mycelium developed in any of the 9 strains studied.

Fermentation of Carbohydrates (14 Days at 37° C.).—Constant carbohydrate fermentations were obtained only after the inoculum had been kept on sugar-free medium for 2 or 3 transplants and when the tubes containing the carbohydrate broth were sealed with vaseline. The following 9 carbohydrates were tested with all

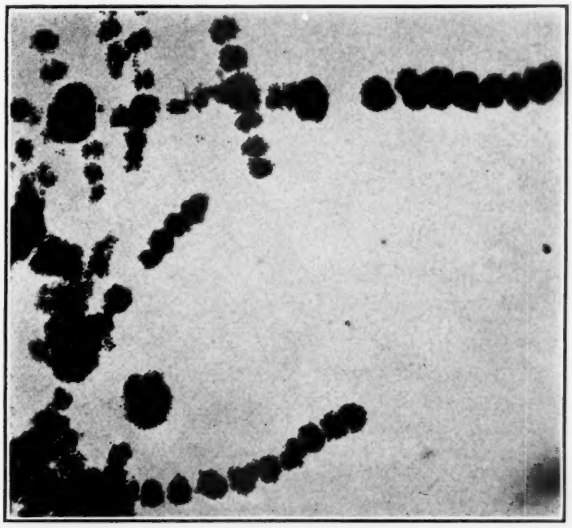

Fig. 4.—Photomicrograph of corn meal agar slide culture of *M. stellatoidea* fixed and stained with lactophenol cotton blue.

strains: dextrose, saccharose, lactose, maltose, levulose, dextrine, galactose, mannite, and inulin. Slight variations in fermentation occurred with some species if the original broth was not titrated to pH 7.2. The ability of each strain to clot milk was tested by the method described by Stovall and Bubolz.[3] Table I lists the fermentations obtained with the various organisms and our results indicate that only the first four sugars need be used. Three organisms, *M. parapsilosis, M. Krusei,* and *cryptococcus* ferment the same sugars, but can be differentiated easily by the other criteria already mentioned.

Ascospore formation: All strains were kept on carrot plugs at room temperature for 60 days before discarding. Smears were made at frequent intervals and examined for asci. None was found in any of the cultures.

Agglutination tests: Numerous agglutination tests were done on most of the strains studied, with various modifications of Benham's[2] technique, and our results agree with those obtained by her. Except for *M. albicans* and *M. candida,* which appeared to be identical antigenically, the other species showed certain antigenic

differences when tested with homologous and heterologous sera which were valuable in confirming the morphologic and biologic findings. The new species *M. stellatoidea*, for example, differed from *M. albicans* in colony formation on blood agar, in morphologic characteristics on corn meal agar and slight differences in carbohydrate fermentation. Justification for the separation of these species was enhanced by the fact that they were quite different antigenically. Agglutination tests are not necessary for identification and the close serologic relationship of certain species of the genus Monilia eliminated this test as a single rapid means of identification.

TABLE I

	DEXTROSE	SACCHAROSE	LACTOSE	MALTOSE	LEVULOSE	DEXTRIN	GALACTOSE	MANNITE	INULIN	MILK
M. albicans (Benham)	AG	A	—	AG	AG	AG	A	—	—	clot
Monilia type II (Stovall)	AG	A	—	AG	AG	AG	A	—	—	clot
Vaginal strains (19)	AG	A	—	AG	AG	AG	A	—	—	clot
M. parapsilosis (Benham)	AG	—	—	—	AG	—	—	—	—	—
Monilia type I (Stovall)	AG	—	—	—	AG	—	—	—	—	—
Vaginal strains (3)	AG	—	—	—	AG	—	—	—	—	—
M. candida (Benham)	AG	AG	—	AG	AG	AG	AG	—	—	—
Monilia type III (Stovall)	AG	AG	—	AG	AG	AG	AG	—	—	—
Vaginal strains (4)	AG	AG	—	AG	AG	AG	AG	—	—	—
M. Krusei (Benham)	AG	—	—	—	AG	—	—	—	—	—
Vaginal strains (4)	AG	—	—	—	AG	—	—	—	—	—
M. stellatoidea n. sp. (29 strains)	AG	—	—	AG	AG	AG	—	—	—	clot
Cryptococcus sp. Vaginal strains (9)	AG	—	—	—	AG	—	—	—	—	—

Pathogenicity.—Previous workers[2, 8] have demonstrated that cultures of *M. albicans* injected intravenously into rabbits cause multiple abscesses and death; five of our strains of this species have been tested with like results. Equal doses of 3 strains of *M. stellatoidea* proved to be incapable of causing abscesses or death in rabbits after intravenous injection.

SUMMARY OF DIFFERENTIAL CHARACTERISTICS

The descriptions given above have been made purposely brief because the criteria of identification have been based on constant differential characteristics obtained by a variety of different methods. A system of identification based on less characteristic variations might be misinterpreted by one not trained in the study of fungi. For example, the chief function of the corn meal agar slide culture is to determine whether or not mycelia are formed and thus differentiate between *monilia* and *saccharomyces* or *cryptococcus*. The structures in the mycelium may be diagnostic when properly interpreted but errors may be made if one relies on this alone. The most important criteria for identification, including only the fermentation reactions of dextrose, saccharose, lactose, and maltose are as follows:

M. albicans: Fairly large dull grayish white colonies on blood agar. Forms acid and gas in dextrose and maltose and acid only in saccharose. Chlamydospores are regularly formed on corn meal agar.

M. parapsilosis: Small round pearly white colonies on blood agar. Forms acid and gas in dextrose.

M. candida: Wide mycelial fringe around colony on blood agar. Bubbly surface growth in Sabouraud's broth. Forms acid and gas in dextrose, saccharose and maltose.

M. Krusei: Wide dry "collarlike" surface growth on Sabouraud's broth. Variation in size and shape of colonies on blood agar. Forms acid and gas in dextrose.

M. stellatoidea: Stellate colony on blood agar. Ball-like clusters on corn meal agar. Forms acid and gas in dextrose and maltose.

Cryptococcus sp.: Meager growth on blood agar. Fails to produce mycelia on corn meal agar. Produces acid and gas in dextrose.

DISCUSSION

The significance of the presence of yeastlike organisms in certain types of vulvovaginitis has been discussed elsewhere.[9] The lack of agreement on methods of identification and suitable terminology has caused confusion and has made it difficult to compare results of the different clinics working on similar problems. A satisfactory agreement is possible only when the technical methods are adapted to the resources of the ordinary hospital laboratory, and when the criteria upon which identification is based are sufficiently distinctive to be obvious to the technician without mycologic training. This has been kept in mind in working out the above procedures for identification. The same methods have been applied with equal success to approximately 100 additional strains of *monilia* isolated from other parts of the human body.

The new species *Monilia stellatoidea,* which is so similar to *M. albicans* when grown on Sabouraud's medium, may be of significance in the interpretation of certain clinical findings. This fungus which occurs frequently in the vagina (43 per cent in our series) has been shown to be nonpathogenic for rabbits and may be a harmless parasite in the human vagina. Many of the yeasts formerly identified as *M. albicans* may prove to be *M. stellatoidea* and thus explain why vulvovaginitis occurs in only about half the patients from which the so-called *Monilia albicans* has been isolated.[9]

According to the rules of botanic nomenclature, a previously undescribed fungus cannot be officially recognized unless a concise Latin description is appended.

Monilia stellatoidea n. sp.: Found in vaginal secretions of pregnant or nonpregnant women. Colonies stellate on beef-extract blood agar incubated at 37° C. for ten days; thick creamy colonies on Sabouraud's dextrose agar at room temperature. Broth clear with heavy sediment. Forms acid and gas in dextrose, maltose, levulose or dextrin; milk coagulated. Large clusters of ovoid and round conidia formed at septations along pseudomycelium on corn meal agar at room temperature; chlamydospores very rare. Nonpathogenic for rabbits.

Habitat in secrementis vaginalibus feminarum praegnantium aut non-praegnantium. Coloniis vescentibus agare carnis atque cruoris, decem dies, aestate 37° C., et formatis

modo stellarum; coloniis agare dextrose Sabouraudis aestate 20° C. vescentibus densis atque gilvis. Vitulium clarum est, faex abundans. Acetum et bullae oriuntur ex vitulio *dextrose, maltose, levulose* aut *dextrin;* lac coagulat. Conidia ovata, rotundata, in septis in pseudomyceliis cumulantur, agare farinae zeae-maydis, aestate 20° C. vescitur; chlamydosporis rarissimus; leporibus non inuriosa.

SUMMARY

Sixty-eight strains of yeastlike organisms have been isolated from the vaginal tracts of 52 pregnant (32 per cent) and 16 nonpregnant (14 per cent) women.

These strains have been identified and compared with type species of Benham and Stovall by developing a technique which can be carried out in a routine bacteriologic laboratory and which does not require special mycologic training.

The procedures necessary for identification are presented and discussed.

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THE BLOOD PICTURE OF PREGNANCY

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SINCE the turn of the century, a tremendous volume of literature has accumulated on the subject of anemia of pregnancy. A résumé of this indicates that a small percentage of women may develop either an hypochromic or pernicious anemia, that a larger group do not deviate from normal, and that a still larger group have a lowering of hemoglobin and red blood cells not of the type that can be classified with the anemias mentioned. It is this latter group of women in whom the controversy arises, whether the change in the blood is physiologic or pathologic. Most authors concede that there is a physiologic change, but there is no concurrence of opinion as to its extent. Sporadic outbursts of enthusiasm for methods of treatment are futile until we settle in our own minds within what limits the blood may normally vary, and what is more important, create a better knowledge of hematology in pregnancy. We prefer the term "blood picture" of pregnancy, to "anemia," in this discussion.

What are some of the factors which may influence the blood picture of pregnancy? The preexisting state of the patient's blood, a diet lacking in the necessary materials for blood formation, changes in the gastrointestinal tract depressing assimilation must be considered. Even more interesting is the effect of the creation of a new, highly vascular organ, the pregnant uterus, on the existing circulation, the fluid changes in the blood stream and tissues, fetal demands, the possibility of increased hemolysis, and the influence of altered glandular function on the hematopoietic system. Some of these factors we may be able to control but others we cannot, nor would we be justified in considering them as needing control. If it is granted that during pregnancy there are influences acting to alter the usual blood picture, we must endeavor to evaluate each one before accepting as fact that lowered hemoglobin and red cell count must mean anemia.

We feel that there should be acceptance of the evidence showing increase in the water content of the blood plasma during pregnancy. Several investigators have presented evidence to prove this change, of whom we would like to mention two.

The work of Van Donk and associates[1] is of considerable interest. Experimenting with rats, they found a consistent "anemia" during pregnancy which was not influenced by forced feeding of high protein, iron, and vitamin content diets and upon studying the fluid changes occurring in the blood, came to the conclusion that increased water content was the cause of the apparent anemia, suggesting this as the probable cause of the same phenomenon in human beings. Oberst and Plass[2] in a recent publication have shown the same fluid changes in the blood plasma of pregnant women. While the degree of the increased water content of the plasma is subject to variation in different individuals, there can be but little doubt that this factor is a major one to explain the lowering of blood values in pregnancy. Hemoglobin and red blood cell levels may be even more markedly lowered by "watering" of the plasma than has been stressed.

Many investigators have made the observation that the "clinic" patient has a lower blood level than the "private" patient and have advanced this as evidence of the adverse effect of improper diet and environment. That diet is a considerable factor cannot be denied, the outstanding example of which is the 3 per cent hospital incidence of pernicious anemia of pregnancy among the women of India, described by Wills,[3, 4] which she has shown to be dietary in origin, particularly referable to long-standing vitamin B deficiency. However, diet can be overstressed and used as a cloak under which to hide our faulty understanding. Nutritional anemia among all classes of patients, exclusive of pregnant women, is of relatively infrequent occurrence in clinic or private practice in this country. By the term nutritional anemia, we mean an anemia based entirely on food ingested and not disorders of assimilation. Why should the pregnant woman, stimulated as she is by pregnancy and usually tending to overeat, be peculiarly susceptible to nutritional

anemia? The influence of diet and environment seems of relatively less importance than the effect of pregnancy per se on the blood picture.

Despite all that has been published, we do not feel that the blood picture of pregnancy has been investigated to the fullest extent. We have made an effort to intensively study our patients not only during pregnancy but for a considerable period thereafter. Our results are at variance with many published and as a consequence, the conclusions differ radically from those generally accepted. That you accept these conclusions is not of as much importance as that the present knowledge of anemia of pregnancy be considered with a healthy skepticism.

METHOD

Our object was to establish data on a sufficiently large group of pregnant women to determine in general their percentage distribution in regard to hemoglobin level both antepartum and postpartum as a basis of discussion. Our next step was to make an intensive study of a smaller group of women, selected from those adjudged anemic by current standards in order to elucidate some of the factors we have previously mentioned as contributing to the blood picture of pregnancy.

The first group mentioned above comprises all confinements in the University hospital during a one-year period, 500 in number. These patients had one or two hemoglobin determinations antepartum and a like number during the postpartum hospital period.

The second group of women, 50 in number, were selected from patients who at the first clinic visit had hemoglobins of less than 70 per cent Sahli. Each patient of this group was instructed to report every two weeks for a hemoglobin determination and red blood cell count. Capillary blood was used at one visit and intravenous blood at alternate visits, the latter for hematocrit readings and blood counts. Gastric analysis was done when the patient would consent. The gastric analysis was of the routine type, using the alcohol test meal, and when no free hydrochloric acid was found, histamine injections were given. Gastric analyses were done as early as possible during pregnancy. A three-day diet record was obtained from the majority of patients, this being in the form of an itemized account of all food eaten during this period as well as the amount. All patients were instructed to take no medication during the period they were under observation and this request was adhered to in every instance. Four patients were treated; these will be mentioned later.

The study was continued throughout the pregnancy and for as long as fifteen months postpartum. Since relatively few of the obstetric patients enter the clinic during the first trimester, our observations did not include this period as a rule. On the tenth postpartum day, while the patient was still in the hospital, an intravenous blood specimen was taken for hematocrit reading and a blood count. We endeavored to have patients return when six weeks postpartum and thereafter at frequent intervals for as long as fifteen months. No effort was made to select patients according to parity, but since the majority of the women attending the clinic are primiparous, primiparas form the largest number in the group.

Hemoglobin determinations were made with the Sahli method, using the Leitz hemometer, calibrated by the acid hematin method, 14 gm. of hemoglobin representing 100 per cent. All pipettes and counting chambers were U. S. standard. Specimens

collected for hematocrit reading were diluted with 1.4 per cent potassium oxalate solution as the anticoagulant. The laboratory work was done in the Hematological Laboratory of the University clinic by a single, trained technician.

DATA AND DISCUSSION

We wish to discuss first the results of the investigation of the group of 500 women. Chart I illustrates the percentage distribution of this group based on hemoglobin values. The majority, 81 per cent, had hemoglobin values of between 55 and 75 per cent Sahli during the antenatal period. That 81 per cent had hemoglobin values as shown seems conclusive evidence of the magnitude of the downward trend of blood levels during pregnancy. Adair, Dieckmann, and Grant[5] in their recent paper on

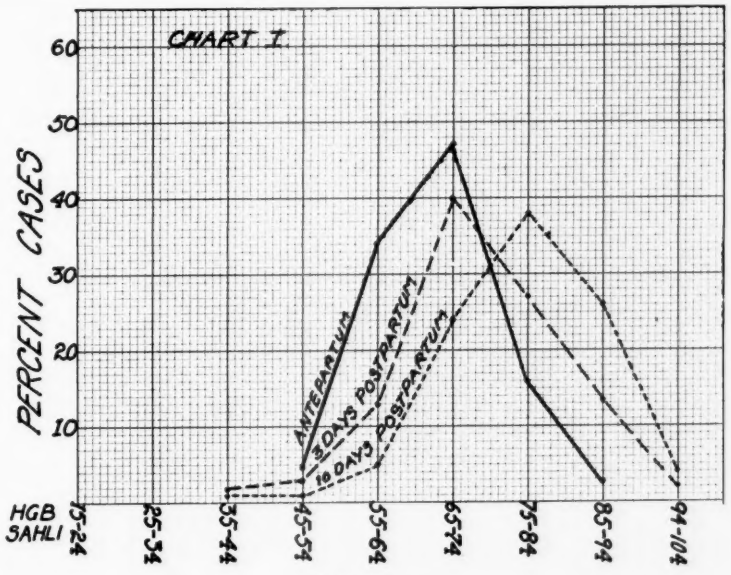

Chart I.

anemia in pregnancy, state that 63.2 per cent of 7,800 women studied had an anemia according to the standards for the nonpregnant, and 11.6 per cent were truly anemic when the standards which they adopted for pregnancy were used. Comparing their statistics to ours, in general there is agreement, but their series shows a greater number of women with better than 70 per cent hemoglobin. Both studies show a preponderance of women with hemoglobin below 80 per cent—63.2 per cent in theirs, 81 per cent in ours. The lower limit of normal for hemoglobin in pregnancy must of necessity be arbitrarily set due to the fundamental lack of knowledge. As a result of the study of a selected group of patients to be discussed later, we place the lower limit of normal at 55 or 60 per cent Sahli. Referring to Chart I again, roughly 5 per cent of our patients had hemoglobins of less than 55 per cent Sahli, which we feel is the probable incidence of true anemia during pregnancy.

A point of peculiar significance to be noted in Chart I is the rather sudden return of the blood to higher levels in the immediate postpartum period. When it is considered that a number of these women had abnormal blood losses at the time of delivery, the phenomenon becomes more remarkable. If the fall of hemoglobin during pregnancy were true anemia, the shift toward normal would be difficult to explain. Instead of an immediate decrease in the number of patients with less than 55 per cent hemoglobin, at least a temporary increase would be expected. One would not look for a favorable reaction from blood loss in the presence, for instance, of a gastric ulcer associated with an anemia, yet the blood loss incidental to delivery does not have the predicted effect

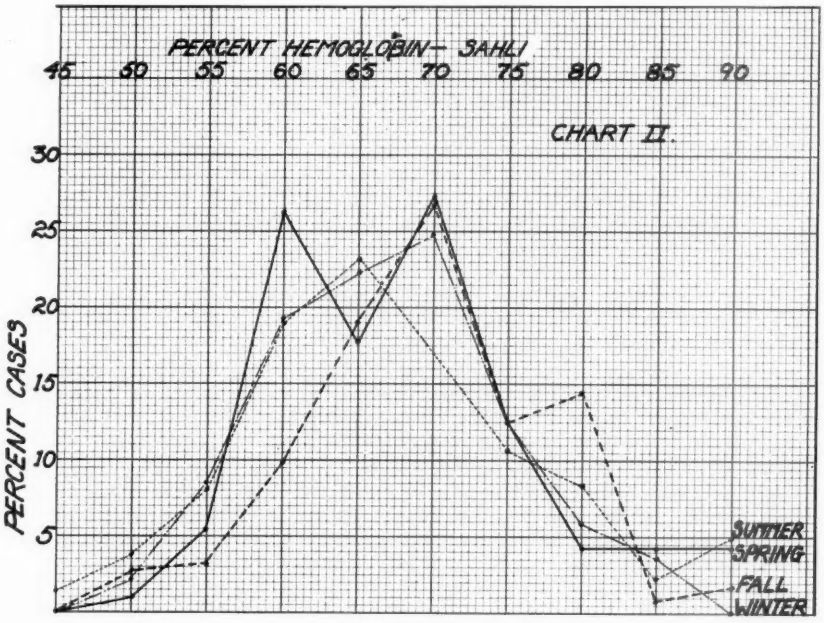

Chart II.

were we dealing with an anemia. The physiologic factors, particularly hydremia, seem to us to become most evident in the explanation of the postpartum reaction of the blood.

Diet and environment as a factor in the blood picture of pregnancy do play their part, but to what degree they cause significant lowering of blood levels is difficult to estimate. Chart II represents the group of 500 pregnancies, segregated into the seasons during which the original hemoglobin and red cell counts were made, in accordance with their percentage distribution based on the hemoglobin. No seasonal variation is apparent, and from this we infer that the variation in available food and sunshine is not of sufficient significance to be reflected in the blood picture of these women. Two-thirds of the selected group of patients

submitted three-day diet lists, and a study of these showed a moderately well balanced diet, not lacking in the essential foodstuffs. While the patients favored carbohydrate in their diet, there was no evidence to show a protein deficiency. Those women having the lowest average hemoglobin during pregnancy had diets indistinguishable from others with higher hemoglobin. We think that only the extremes of poverty, adverse living conditions and perversity of appetite are appreciably reflected in the blood picture of pregnancy.

Our discussion now turns to the group of 50 patients selected for special study and observation of the blood uninfluenced by treatment. Of the 50 women, 10 have been excluded as the basis of data for charts;

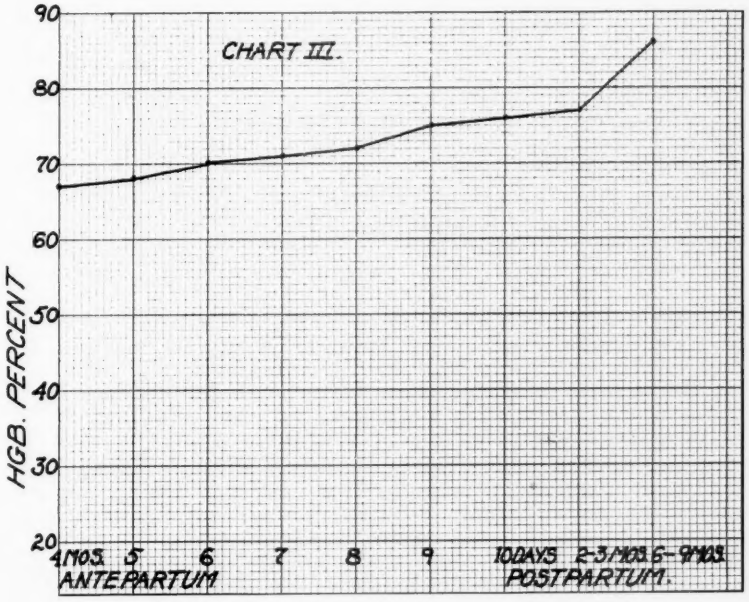

Chart III.

4 because they were given treatment, 2 having hypochromic anemia, 1 the blood picture of pernicious anemia, and a fourth, who was treated in error. The other 6 were excluded because only the first hemoglobin was less than 70 per cent.

Chart III represents the average hemoglobin reading of this group of women antepartum and postpartum. From the fourth month on, a steady upward climb of the hemoglobin level is noted, being at term only slightly less than normal (77 per cent). At six to nine months postpartum a normal level is reached, but even at ten days postpartum the hemoglobin is practically normal. When it is considered that these women were selected because of hemoglobin below the accepted lower limit of normal for pregnancy, the chart is unusual. One might expect that in this group there were those whose hemoglobin did not rise during

the antenatal period. This was true of a few, but in only one case was the drop as term approached appreciable. The exception was a patient who had an exacerbation of a chronic pyelitis during her pregnancy. The hemoglobin dropped to 50 per cent at term, but one month postpartum without treatment was 80 per cent. If the drop in blood level is pathologic, the maximum fall in hemoglobin should coincide with the maximum development of the products of conception. Studies by Coons[6] have shown that the demands of the fetus for iron are increasingly greater as term is approached. Our data do not demonstrate the relationship between the mother's hemoglobin and the changing fetal requirements.

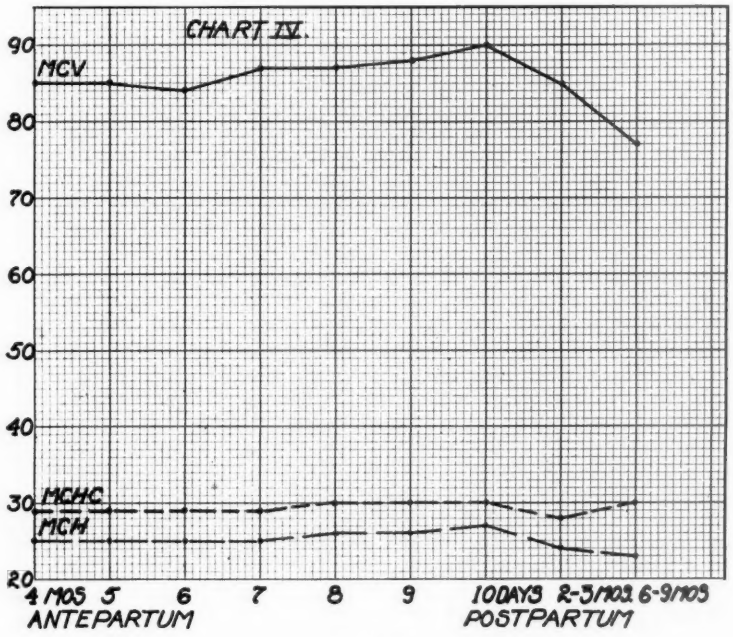

Chart IV.

In a relatively large percentage of the group, a spectacular rise of the hemoglobin to normal was noted in the last trimester. A precipitous rise of the hemoglobin from 55 or 60 per cent to 90 per cent or over dispelled any idea that we were dealing with an anemia. We noted that those patients whose hemoglobin rose to 90 per cent or over before delivery maintained that level postpartum, whereas those whose level at term was below 80 per cent, would, after delivery and as much as fifteen months postpartum, not develop more above 80 per cent. From this we advance the idea that there are in general two groups of patients to be considered, those who in the nonpregnant state have high normal hemoglobin and those who have low. Obviously, if a woman normally has 95 per cent hemoglobin and drops to 70 per cent during pregnancy, then

one whose hemoglobin is 80 per cent might be expected to drop to a variable degree below 70 per cent, since the same factors are operating in each case. It is interesting to note that none of the patients were anemic six to nine months postpartum. Two had given histories of anemia antedating their pregnancy, but neither of these women proved to be so during the many months they were observed after delivery. We can safely state that pre-existing anemia was not a factor in the blood picture of these women during pregnancy, if the resumption of normal hemoglobin after delivery is accepted as evidence of their usual hemoglobin level.

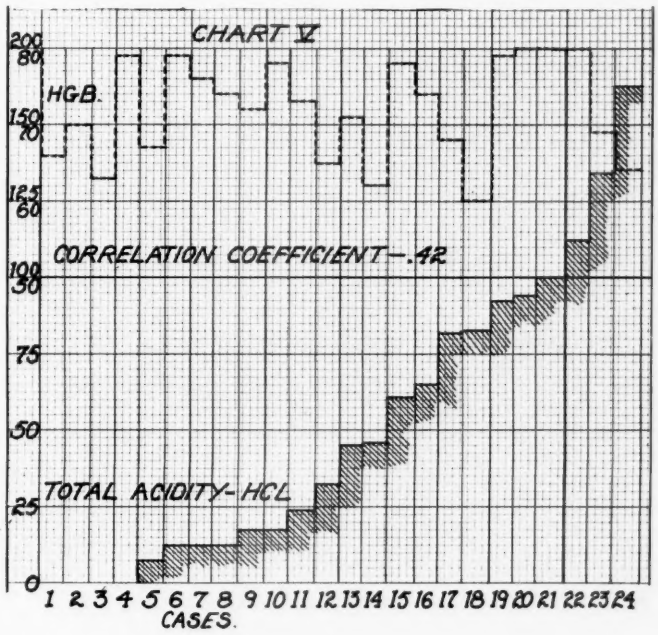

Chart V.

Consideration of the hematocrit readings reveals an interesting point. As shown in Chart IV, which gives the average mean corpuscular hemoglobin, corpuscular volume and corpuscular hemoglobin concentration, antepartum and postpartum, of 40 cases, the general level of the calculations falls within the normocytic range of Wintrobe.[7] Six to nine months postpartum, despite the return of the hemoglobin and red cell count to normal, there is a tendency toward the microcytic range. At nine months postpartum, the effect of pregnancy can be said to have disappeared. Comparison of the ante- and postpartum figures gives no evidence of any considerable disturbance of the hematopoietic system, but does demonstrate an even greater resistance of the blood picture to deviate from normal during pregnancy than during the remote postpartum period.

In the study of the gastric analyses performed upon 24 of the women, it was hoped that the factor of faulty food assimilation due to altered gastric secretion might be demonstrated. In Chart V, the lower graph represents the total acidity of the four specimens of each patient. The upper graph shows the average of all hemoglobin readings for the same patient throughout the antepartum period. A total free hydrochloric acid content in four specimens of 100 has been taken as the lower limit of normal. Four patients were normal and a similar number had an achlorhydria; 73.4 per cent of the series had a low hydrochloric acid secretion. The striking similarity of results published by Strauss[8] who studied a similar number of women, reporting 75 per cent with less than normal hydrochloric acid secretion during pregnancy, is worthy of mention. An effort to correlate the average hemoglobin reading and the gastric acidity of each patient resulted in a correlation coefficient of 0.42, too low to prove a direct relationship. Gastric analysis did not prove a diagnostic aid in predicting the course of the hemoglobin level during pregnancy. Further efforts to prove a relation between altered assimilation of food during pregnancy and its bearing on the blood picture will require more detailed study of gastric secretion than is obtained by this procedure.

Routine estimations of the icteric index were made from the hematocrit specimens. The readings were from 2 to 7.5; two patients had icteric indices as high as 10 on one occasion. Since the icteric index did not tend to deviate from normal, we cannot say from this laboratory procedure that there is evidence of increased hemolysis during pregnancy.

While we think that it is possible for the hemoglobin to drop to 55 per cent during pregnancy and represent a purely physiologic change, we do feel that any patient with less than 60 per cent hemoglobin should be investigated and an hypochromic or other type of anemia ruled out. Our experience is that specific anemias will usually result in a hemoglobin of less than 55 per cent early in pregnancy, certainly by the fourth month.

CONCLUSIONS

1. The majority of pregnant women have a lowered hemoglobin and red blood cell count which is physiologic and its extent influenced by the hemoglobin level in the nonpregnant state.

2. The physiologic lowering of the hemoglobin during pregnancy may reach 55 per cent Sahli (7.7 gm. hemoglobin per 100 c.c.).

3. Patients with true anemia will present the picture relatively early, certainly in the first half of pregnancy.

4. The magnitude of the problem of anemia of pregnancy is not as great as that generally stated, and probably is in the neighborhood of 5 per cent.

5. Study should be concentrated on those patients with hemoglobins of less than 60 per cent if our present knowledge of anemia in pregnancy is to be extended.

I wish to thank Mrs. K. Purviance, A.B., for her kind interest and technical assistance in the preparation of data presented in this paper.

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THE QUANTITATIVE DETERMINATION OF ESTROGENIC SUBSTANCES IN NORMAL FEMALE URINE DURING THE MENSTRUAL CYCLE*

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IN RECENT years a number of assays have been made of estrogenic substances in the urine of pregnant and nonpregnant women.[1-7] Allen and his coworkers have recently reported an analysis of the urine of the chimpanzee during the various stages of the menstrual cycle.[8] These attempts to devise methods for an accurate quantitative assay of the estrogenic materials in normal female urine have been carried out in the hope that a basis might be obtained for the analysis of pathologic conditions such as sterility, amenorrhea, oligomenorrhea, menorrhagia, and also possibly uterine fibromyomas.

We now know that an accurate assay of the estrogens in urine depends on many factors, among which the following must have particular attention.

1. Faithfulness in collecting twenty-four-hour samples. This is especially difficult because of the inconvenience the average normal woman finds in saving all of the urine during the day. For this reason we have made some attempts to assay twelve-hour nocturnal samples.

2. Completeness of extraction. It is well established that the estrogens may occur in the form of conjugated compounds such as the glucoronate,[9] which are insoluble in immiscible solvents, such as ether, benzene, and chloroform. These

*This investigation was aided, in part, by a grant from the National Research Council, Committee on Problems of Sex.

compounds are hydrolyzed by boiling for two hours after adjusting the pH to approximately 0.7. This is accomplished by adding 10 c.c. of concentrated hydrochloric acid to each 100 c.c. of urine.

The extraction depends on the size of the droplets of the solvent passing through the urine, the length of the urine column and the time of extraction. The apparatus illustrated by Fig. 1 has given satisfactory results in our hands. In order to avoid diluting the urine, the diameter of the tube containing the urine is varied according to the size of the sample as follows:

VOLUME OF SAMPLE IN C.C.	INSIDE DIAMETER OF EXTRACTION TUBE IN MM.	LENGTH OF EXTRACTION TUBE IN CM.
500	35	75
1,500	50	75
3,000	75	75
4,500	85	75

The distributor is made from sintered Pyrex glass as described by Kirk, Craig, and Rosenfels.[10] Our extractions are carried out for a twenty-four-hour period, during which time approximately 80 liters of chloroform pass through the extraction column. Chloroform has been used in our work because of the fire hazard attached to benzene or ether. In our experience the use of a small gas flame has been very satisfactory.

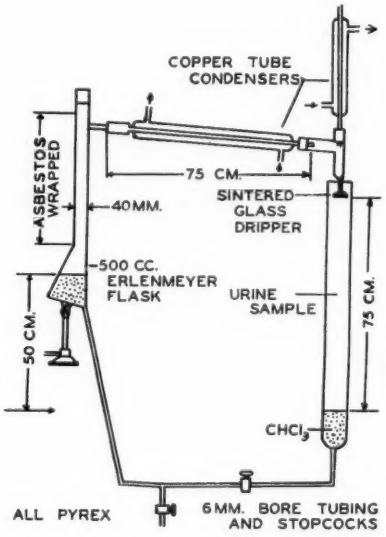
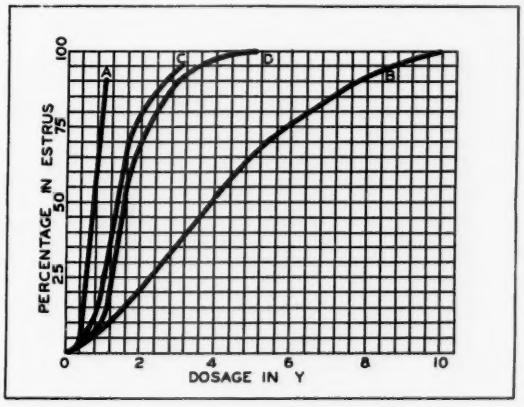


Fig. 1.

3. Partial purification without loss of active principles. Our procedure follows: The chloroform extract with the washings is evaporated to dryness on a steam bath. The chloroform is recovered. The residue is transferred to a 150 c.c. Erlenmeyer flask with alcohol. The alcoholic solution is evaporated to a volume of about 5 c.c. and transferred to a liter separatory funnel. The flask is washed with three portions of peroxide free ether, using a total of 100 c.c. of ether; then once with 10 c.c. of alcohol and finally with 25 c.c. of ether. The ether-alcohol solution is now shaken with 400 c.c. of 8.5 per cent sodium acid carbonate solution. The aqueous layer is separated and is then extracted three times with 100 c.c. por-

tions of ether. The ether extracts are combined and evaporated to dryness. The residue is then taken up in 15 c.c. of 95 per cent ethyl alcohol. This constitutes the *stock solution* for assay.

4. Method of assay. The most satisfactory assays that have been developed to date are modifications of the method of Allen and Doisy,[11, 12] using the vaginal smear of the spayed rat. Workers differ slightly in what they regard as a positive reaction. We have used the full estrous smear; squamous epithelial cells and the practically complete absence of leucocytes. The work of Coward and Burn[13] and Gustavson and D'Amour[14] has shown that the accuracy of the assay depends on the number of animals used. This accuracy also depends on the method of administration of the materials for assay. This phase of the problem has been carefully studied by Marrian and Parkes[15] and by D'Amour and Gustavson.[16, 17] Two methods are in common use: (a) suspending the material in oil and injecting the material in one dose, and (b) suspending the material in water and dividing the dose between several injections. The latter method is the most sensitive and precise. We have used both methods.



INTERNATIONAL STANDARD MATERIAL
A- DOSE GIVEN AQUEOUS SUSPENSION IN FOUR INJECTIONS TWELVE HOURS APART.
B- DOSE GIVEN IN AQUEOUS SUSPENSION IN ONE INJECTION.
C- DOSE GIVEN IN OIL IN ONE INJECTION.
D- DOSE GIVEN IN OIL IN FOUR INJECTIONS TWELVE HOURS APART.

Fig. 2.

Our aim has been to report the estrogenic materials in International rat unit equivalents. The I.R.U.E. is defined as that amount of estrogenic material having the same biologic activity as 0.1 gamma of keto-hydroxy estrin, when the spayed rat is used for the assay. Fig. 2 shows the standardization curves for International standard estrin by four different methods of assay, using fifty spayed rats for each point on the curve. The curves were obtained as follows:

A. The dose indicated was injected in aqueous suspension in four portions at twelve-hour intervals. In making the suspension di-glycol stearate (0.2 gm. in 30 c.c.) was used. Smears were taken twelve hours after the last injections and three more smears were made at eight-hour intervals.

B. The dosage indicated was given in one injection in aqueous suspension. The readings were taken thirty-six hours later and then three more smears at eight-hour intervals.

C. The dosage indicated was given in olive oil in one injection and smears were taken as in "B".

D. The dosage indicated was given in olive oil in four injections at twelve-hour intervals and smears were taken as in "A".

Figs. 3 and 4 show some of our earlier assays of two succeeding menstrual cycles in which the *stock solution* from twenty-four-hour samples was evaporated to dryness and the residue suspended in 33 c.c. of olive oil. These urines were not hydrolyzed before the extractions were made. The material was injected into thirty rats. Each rat received 1 c.c. The urine was collected by a married woman (Mrs. R. G.), aged forty-four years, a bipara with normal menstrual history. It is interesting to note a peak in the excretion thirteen to fourteen days preceding the onset of the next menstrual period and a second peak within a few days of the next period. In order to make sure that the peaks were not vagaries of the extraction procedure, the total lipins were determined, and Fig. 3 shows no appreciable rise

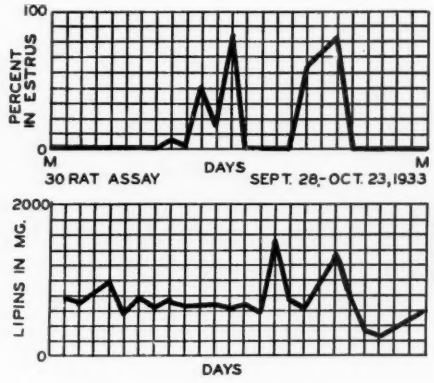


Fig. 3.

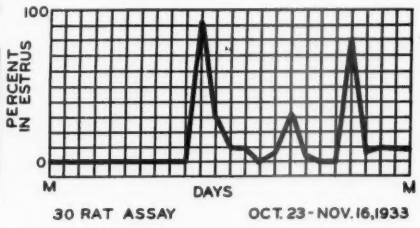


Fig. 4.

in the lipins at the peaks of estrogenic excretion. The estrin content at other times during the cycle was not sufficient to bring any animals into estrus when thirty animals were used for the assay. These graphs are typical of 17 that were obtained by this method.

Series K.: Mrs. A. B., aged forty-four, bipara, with regular and normal menses collected twenty-four hour samples. The urine of this series was not hydrolyzed. The residue from each day's extract was dissolved in 15 c.c. of 95 per cent alcohol.

Five cubic centimeters were reserved for a colorimetric assay which will be reported later. The remaining 10 c.c. were evaporated to dryness and emulsified with 60 c.c. of water and 0.2 gm. of di-glycol stearate. Ten rats were given four injections of 0.5 c.c. If all the rats showed positive smears, 22 c.c. of the solution were diluted with 11 c.c. of water and this was injected into 15 rats in the same way. Fig. 5 is the result of this assay. Again two peaks were found and this time the peaks were observed at twenty and fifteen days before the onset of menstruation.

Series K-2: Same subject as K. In this series it was hoped that an assay could be made of the twenty-four hour sample for the free and combined estrin. One-half of the sample was hydrolyzed by boiling with hydrochloric acid at pH of 0.7. The two portions were then extracted separately and the assay made as under

K. The quantity of uncombined estrogens in the unhydrolyzed portion was so small that practically no response was obtained. Further attempts will be made to determine the free and combined estrogens in twenty-four-hour samples. From the study of the hydrolyzed portion Fig. 6 resulted. In this cycle the peaks of excretion

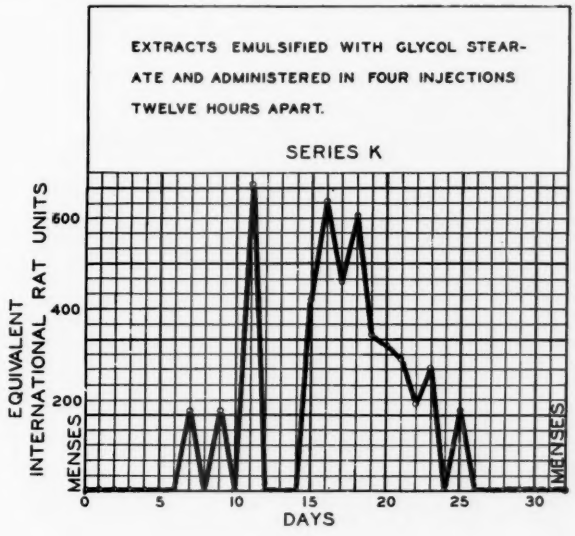


Fig. 5.

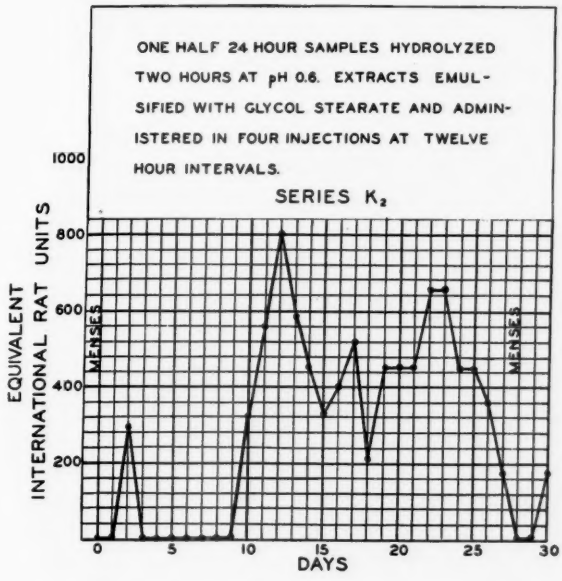


Fig. 6.

came sixteen and six days before the onset of menstruation. Fig. 5 showing the results of the assay of a twenty-four-hour nonhydrolyzed sample, and Fig. 6 showing the results of the assay of one-half of the twenty-four-hour hydrolyzed sample are very similar in form, from which it may be tentatively concluded that the amount

of estrogen in the hydrolyzed sample is increased but the relative excretion from day to day seems to be the same. All the results in this paper are calculated to a twenty-four-hour basis.

The most accurate method we have been able to devise after studying the problem for the past four years is as follows:

Six cubic centimeters of the 15 c.c. of *stock solution* are placed in a small mortar, 0.2 gm. of di-glycol stearate added and the mixture evaporated to dryness on the steam bath. Twenty-seven cubic centimeters of hot water are added in four portions and the mixture stirred thoroughly and the emulsion transferred to a large 20 mm. by 250 mm. test tube to which a stopcock has been sealed. These suspensions are then thoroughly shaken for fifteen minutes in a shaking machine. Very stable emulsions are formed. By drawing the emulsion into the syringe through the stopcock, foam is avoided. This material is injected into 10 rats, each rat receiving 2 c.c., divided into four doses of 0.5 c.c. The injections are made twelve

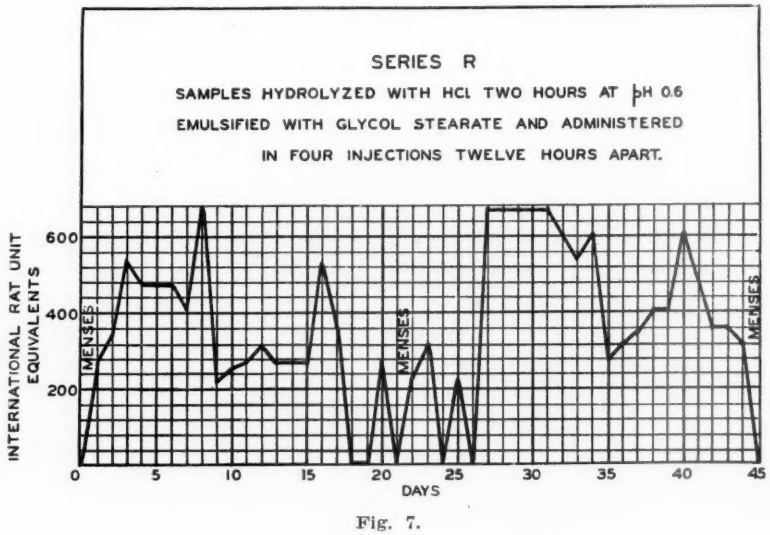


Fig. 7.

hours apart and the first readings taken twelve hours after the last injection. Three more readings are then taken at eight-hour intervals. The procedure from this point depends upon the response obtained. (a) If none of the animals respond, the remaining 9 c.c. of the *stock solution* are evaporated and suspended in 27 c.c. of water in the same manner as described, this dose being 1.5 times the original dose. This material is then injected into 10 rats. (b) If 4 to 8 rats give a positive response to the first injections, the remaining 9 c.c. of the *stock solution* are suspended in 40.5 c.c. and injected into 15 rats; this dose being the same as the original dose. (c) If all of the rats receiving the first injection respond positively, the remaining 9 c.c. of the *stock solution* are evaporated and suspended in 60 c.c. of water and injected into 20 rats in 4 doses of 0.5 c.c., this being one-half the original dose. Figs. 7 and 8 were obtained by this method.

Sample calculations of the amount of estrin in International rat unit equivalents are as follows: (a) 0.2 gm. of di-glycol stearate was added to 6 c.c. of the *stock solution,* containing the extract from a twelve-hour urine sample, and the solution evaporated to dryness. The residue was emulsified with 27 c.c. of water. This

material was injected into 10 rats, each rat receiving four injections of 0.5 c.c. Six of the animals came into estrus. In order to increase the accuracy of the assay, the remaining 9 c.c. were emulsified in the same manner with 40.5 c.c. of water. This gives the same concentration as in the exploratory assay. This suspension was injected into 15 rats in four injections of 0.5 c.c. Ten of the rats came into estrus, making a total of 16 out of 25, or 64 per cent. This corresponds to 0.82 gamma of International standard estrin per rat from Curve "*A*", Fig. 2. This is equal to 8.2 rat units. The number of International rat unit equivalents therefore, since 2 c.c. are equal to 8.2 International rat unit equivalents and the material was placed in 67.5 c.c., is $\frac{67.5 \times 8.2}{2} = 276$, or if we assume the excretion for twenty-four hours to be twice that of twelve hours, the twenty-four-hour excretion is 552 International rat unit equivalents. (b) Six cubic centimeters of the *stock solution* of another extract of a twelve-hour sample were emulsified and injected into 10 rats as described in (a). None of the rats came into estrus. This makes

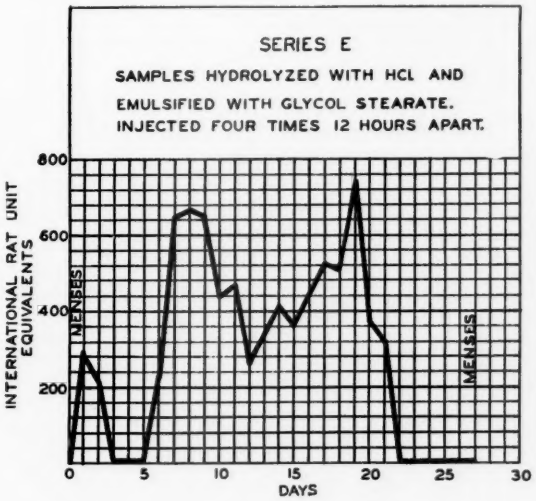


Fig. 8.

it necessary to use a higher concentration of the material. The remaining 9 c.c. of the *stock solution* were emulsified with di-glycol stearate in 27 c.c. of water and injected into 10 rats. Four rats out of the 10 came into estrus. Forty per cent corresponds to 0.65 gamma of International standard estrin per rat from the standardization curve, which equals 6.5 rat units. This amount was contained in each 2 c.c. of the 27 c.c., but this was only 9/15 of the total *stock solution*. The number of International rat unit equivalents is therefore $\frac{6.5 \times 27 \times 15}{2 \times 9} = 146$ or 292 for a twenty-four hour sample.

Fig. 7 shows the excretion curve obtained by this method of assay of urine, collected for twelve hours during the night from the same woman who contributed the urine for Figs. 3 and 4.

Fig. 8 shows the excretion from an unmarried girl (Miss R. E.), twenty-two years of age, using twelve-hour nocturnal samples. This girl had a normal menstrual history.

In the present state of our knowledge, the interpretation of these graphs, so far as they reflect, or are the result of, what is taking place in the endocrine system during the sex cycle, can only be speculative.

The thing which impresses one, as the graphs are viewed side by side, is that in each case, there are two peaks of estrin excretion, and by inference two peaks of estrin concentration in the blood. In some, this peak is sharp and reaches its maximum in one twenty-four-hour specimen. Less frequently a maximum is shown over a period of two days or more. After the first peak, there is a drop of varying degree, followed by another peak, and in every case the estrin excretion drops to zero at or very shortly preceding the next ensuing menstrual period.

In studying these graphs over a period of several years, we have come to think that the first peak is coincident with ovulation. We believe, however, that this point remains to be proved. It seems reasonable to believe that this peak represents the height of follicle activity, and that when it ruptures there is either a cessation or considerable diminution of its cellular activity. For a varying period of time following its rupture, before the growth of the lutein cells, one would expect a drop of estrin production. In the graphs, such a drop follows in every case the appearance of the first peak.

After the lapse of a certain amount of time, the structure is converted into the corpus luteum. We know that while this body is responsible for the formation of progesterone, it is also responsible for the continued formation of estrin[18, 19] to as great, if not to a greater extent, than the follicle before rupture. If this is so, it could account for the second estrin peak which is present in all of the graphs. The regression of the corpus luteum, with a diminution or disappearance of estrin is followed shortly by menstruation. This coincides with our knowledge of the action of estrin when given to the human female after castration, viz., that bleeding follows the withdrawal of estrin, if the amounts administered were sufficient.

The graphs shown are those of three women, all entirely normal from gynecologic and general standpoints. Since a particular ovulation and developing corpus luteum are the controlling factors in the next subsequent menstruation, it is of interest to note what relation the peaks in the graphs bear to the time of the next menstrual period in each case. It can be seen that neither of the two peaks bears any constant relation to the time of the next menstruation, nor do they to each other. This variation is seen in the graphs of different individuals and in different cycles in the same individual.

It seems to us that these observations necessitate one of two conclusions: (1) either the time of ovulation may vary considerably from cycle to cycle in the same individual, and be considerably different in different individuals, and that the corpus luteum may require varying

periods of time to reach its full development and activity, or (2) the peaks of estrin excretion, presuming peaks of concentration in the blood, have no particular relationship to ovulation and corpus luteum activity. With the constancy with which these two peaks appear in the graphs used for these illustrations, as well as in all others obtained from daily twenty-four-hour specimens in normal individuals, the first conclusion seems to be more logical.

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A STUDY OF 285 CASES OF BREECH DELIVERY*

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THE fetal mortality attending breech delivery is far greater than that which accompanies deliveries in the cephalic position. We have studied the cases of breech presentation occurring in 8,531 cases in the department of obstetrics and gynecology in the Evanston Hospital. These numbered 285, an incidence of 3.34 per cent. This indicates a frequency slightly in excess of that usually quoted, which is 3 per cent. We have studied this series of cases to find out exactly what our results have been, and, if possible, to ascertain whether our results might not be improved. The fetal mortality in various reports and textbooks ranges from 7.6 per cent to 15 per cent at term. Many premature infants, not yet viable or so near the lower limit of viability that life expectancy is slight, are delivered as breech presentations. Little can be done to decrease the loss of life in this group as it is

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due almost wholly to insufficient preparation for extrauterine life and only slightly to obstetric trauma. We are particularly interested in discovering what may be done to lessen the loss of fetal life among the group of infants who have completed the term of intrauterine life and are prepared for independent existence.

TABLE I. INCIDENCE

Total deliveries	8,531
Breech	285
Babies	293
Incidence	3.34%

If a breech position is discovered as the pregnancy advances into the third trimester, what is the wisest course to pursue? Opinions have varied, one group advising that all breech positions be changed to cephalic, while another feels that they should be let alone, labor being permitted to begin with a breech presentation. Our position in this matter agrees with neither of the above. We rather definitely think, at about the end of the eighth month, that an attempt at external version should be made. This is done with the foot of the table elevated so that the breech may gravitate upward away from the inlet. Prior to labor the breech is rarely engaged. If, with the use of reasonable force the breech may be converted to a head position, we believe that the version should be carried out. We do not use anesthesia, believing that with the patient anesthetized, there is a tendency to use more force than is wise. If much force is needed, and after the exertion of moderate pressure upon the fetal poles the fetus fails to turn, the attempt is given up. There has been some difference of opinion as to the danger of the use of considerable force. We believe that there is sufficient danger to the child from drawing tight, loops of cord which may be about the neck or extremities, to warrant our rather conservative attitude. The delivery of a multipara of a child of moderate size in the breech position is often easy, and it does not seem wise to relieve the infant of a slight risk only to subject it to a greater one.

We much prefer that labor should begin spontaneously. Induction is only done when a rather clear-cut indication exists. We much prefer to have the membranes remain intact until dilatation is complete, or nearly so, although our experience has been that an early rupture is more frequent in breech cases because of the deficient filling of the lower uterine segment by the breech. The first stage in breech labor may be longer than in cephalic presentation and dilatation should be allowed to complete itself without interference. The use of some effective form of analgesia is often of great value.

In cases of frank breech we greatly prefer to allow the breech to descend and for the hips to be delivered by the force of the uterine contraction, aided, if possible, by the voluntary efforts of the mother, before intervening. From that point on extraction by the method of Mauriceau is done. This is varied in some cases in that we may adopt the suggestion of Potter and deliver the anterior arm first. This we find in some cases to be an excellent maneuver, as the anterior arm is swept to the back as it is freed from the birth canal, thus bringing the shoulder and arm which was originally posterior to the front. The second arm is then often delivered with ease.

If this method is not easily applicable the older technic of freeing the posterior arm first is used. A common error is failure to continue extraction of the body of the infant until the tip of one scapula is visible. Attempts to deliver the arms before this time are likely to be far more difficult. We have found that two assistants to hold the legs of the mother is a much more satisfactory arrangement than the use of stirrups. These are objectionable upon three grounds: first, the thighs are so sharply bent upon the abdomen that it is difficult to follow down the fundus with the hand and more difficult to assist delivery by pressure upon the head above the symphysis. Second, the perineal structures are rendered more tense, and third, the pelvic inlet is slightly decreased in its anteroposterior diameter. If the thighs are held at an angle of about 130 degrees the operation is more conveniently done.

In cases of full double footling breech, especially if the feet come down into the vagina, intervention may be begun earlier.

In this series of 285 breech deliveries, the pregnancies varying in length from five months to term, there were 55 fetal deaths, or 18.8 per cent. Many premature infants are born in breech presentation. In this series there were 27 cases in which the fetus was of less than seven months' gestation.

The mortality in this group was 96 per cent. The chance of survival of infants of under seven months or of less than four pounds weight is so slight that we exclude them in estimating the mortality justly chargeable to obstetric technic. In the group of infants of over seven months' gestation were six monsters, none of which survived, and one macerated fetus which had died in utero before the onset of labor.

There were 188 cases of breech presentation in patients at or near term. In this group there were 11 fetal deaths, a neonatal mortality of 5.85 per cent.

A very marked difference is found if mortality of infants weighing five pounds or more is compared with that of infants under five pounds. The premature infant stands the trauma of operative delivery far less

well than does the infant of normal size, and is also not as fully prepared for extrauterine life. In 187 cases, one infant weighing five pounds or more was delivered while in 20 others a twin weighing over five pounds was delivered by the breech. In these 207 deliveries there

TABLE II. FETAL DEATHS

Premature (under 7 mo.)		27
Deaths		26 or 96%
Macerated fetus		1 death 1
Monsters		6 death 6
Twins		30—60 babies
36 delivered as breech		
9 lost	25%	
Term	188	Deaths 11—5.85%

were 18 deaths. Three of the infants which were lost were monsters. If these are excluded and the anatomically normal infants only considered, we find a mortality in this group of 7.3 per cent. In 40 cases in which the infants weighed less than five pounds there were 27 deaths. Three of these were monsters. Excluding the monsters and considering only the anatomically normal infants, we find a mortality of 64.8 per cent. The child which is near the end of gestation withstands the strain of delivery and that of independent existence far better than the premature infant.

TABLE III. INFANT MORTALITY—BREECH DELIVERY

WEIGHT	NO. CASES	MORTALITY	MONSTERS
Single Deliveries			
5 pounds and over	187	15	3
Under 5 pounds	24	18	2
Weight unknown	8	7	
Twin Deliveries			
5 pounds and over	20	0	0
Under 5 pounds	16	9	1
Weight unknown	-	-	-

A study was made of the influence of the infant's weight and the length of labor upon the neonatal mortality. The primiparas and multiparas are considered separately. Among the primiparas, of whom there were 94, with the exception of the group of very large infants, those weighing from 9 to 10 pounds, no great influence can be noted. While the group of very large infants is too small to be conclusive, there was one fetal death in five cases, a mortality of 20 per cent.

In the group of multiparas the lowest mortality appears in the group of large babies, those of 9 to 10 pounds in weight. In this group the lowest mortality is found in the subgroup of infants weighing 7 to 8 pounds. Among this number occurred a labor of twenty-seven hours, the longest recorded among the multiparas.

An attempt has been made to estimate the loss of blood. Seven multiparas and 3 primiparas lost an amount estimated to be over 500 c.c. Sixty-three of 111 primiparas and 67 of 116 multiparas lost between 200 and 400 c.c. Packing of the uterus to control bleeding was done in the cases of 5 primiparas and 3 multiparas. The frequency of packing is probably greater than it would be in many other institutions, as we very definitely believe that packing should be done

TABLE IV. DURATION OF LABOR. MULTIPARAS

WEIGHTS	CASES	LONGEST	SHORTEST	AV. LABOR	FETAL MORT.
6- 7	27	16°	2° 15′	6° 8′	5
7- 8	24	27°	2° 30′	9° 12′	1
8- 9	18	17°	1° 37′	7° 8′	2
9-10	8	19° 45′	1° 16′	6° 23′	

TABLE V. DURATION OF LABOR. PRIMIPARAS

WEIGHTS	CASES	LONGEST	SHORTEST	AV. LABOR	FETAL MORT.
6- 7	38	34°	4° 30′	13° 33′	3
7- 8	25	55° 23′	2° 14′	14° 18′	1
8- 9	26	70°	2°	16° 21′	2
9-10	5	25°	6° 45′	17° 15′	1

early in the course of bleeding rather than late and that the preservation of the patient's own blood in her circulation is far better than the introduction of that of another individual after uncontrolled bleeding has created a serious anemia. A survey of the figures in Table VI does not indicate that a breech delivery is accompanied by a greater blood loss than a cephalic presentation. Loss of blood in breech deliveries is influenced, as in other cases, by exhaustion of the mother which causes the uterine muscle to act less efficiently, by relaxation of uterine musculature because of deep anesthesia, and by operative injuries. Attempts at delivery before dilatation is complete are especially likely to produce deep cervical injury which may cause bleeding.

TABLE VI. AMOUNT OF BLEEDING ALL CASES

	MULTIPARAS	PRIMIPARAS
Under 100 c.c.	15	15
100-199 c.c.	34	22
200-299 c.c.	29	45
300-399 c.c.	11	15
400-499 c.c.	5	8
Over 500 c.c.	7	3
Amt. not given	5	5
Uterus packed	5	3

All cases in which the infant weighed more than six pounds have been studied to ascertain what influence upon neonatal mortality is

exercised by the use of various anesthetics or analgesic drugs. The lowest mortality, 2.5 per cent, was found in the group of cases in which pentobarbital-sodium and scopolamine had been used as analgesics. Although we have used this combination extensively and have been pleased with our results, we do not maintain that these drugs protect the infant from the dangers of labor. We do believe that it is rather clearly shown that the administration of these analgesic agents does not increase the risk to which the infant is subjected. The maternal and neonatal results have been studied by one of us (C. E. G.) in two series of cases in which sodium-pentobarbital scopolamine was used. In a group of 96 women to whom no analgesic drugs were given, the mortality was 10.4 per cent, a greater neonatal loss of life than occurred with any form of analgesia or anesthesia. Those cases in which morphine or pantopon was used yielded the next highest infant mortality, 8.16 per cent. In order justly to assess the

TABLE VII. ALL BABIES WEIGHING OVER 6 POUNDS (185)

	CASES	MORTALITY	PER CENT
No drugs	96	10	10.4
Morphine	49	4	8.16
Pentobarbital	40	1	2.5
Drop ether	109	10	9.1
Gas	59	4	6.7
No anesthesia	14	1	7.1

influence of these drugs upon the infant mortality rate it would be necessary to study each history separately. Weighing all cases by the same standard it appears that the newer method of analgesia cannot be accused of increasing the neonatal death rate in breech cases. The death rate in cases in which drop ether was used, 9.1 per cent, seems high. It is probable that it is not wholly chargeable to the ether. This anesthetic is often used in cases in which some difficulty in delivery is anticipated.

Our cases were divided according to the type of delivery. In this tabulation all cases were included. Spontaneous delivery, in primiparas, including those delivered by manual aid, and breech extraction showed essentially the same mortality, 22 per cent and 23 per cent respectively. In this series, decomposition of the breech, followed by extraction, gave no mortality at all. In those cases in which the breech was decomposed a marked variance is found between the mortality in primiparas and in multiparas. Eighteen cases occurring in primiparas were so treated without the loss of a single infant. The same procedure, done upon 8 multiparas resulted in two fetal deaths, a mortality of 25 per cent.

Thirty-four women were delivered by cesarean section. It has been suggested that a breech presentation in a primipara constitutes an in-

dication for abdominal delivery. With this we do not agree. We believe that a reasonable indication exists when there is disproportion, caused either by a small pelvis or a large infant, so that the chance of delivering a living and uninjured baby through the birth canal seems less than normal. The great majority of our cases of breech presentation, including primiparas, were delivered without recourse

TABLE VIII. TYPE OF DELIVERY—MORTALITY

	MULTIPARAS			PRIMIPARAS		
	CASES	FETAL MORT.	PER CENT	CASES	FETAL MORT.	PER CENT
Spontaneous	28	7	25	9	2	22
Breech ext.	94	16	17	101	24	23
Breech broken up	8	2	25	18	0	0
Cesarean	6	1	16	29	3	10
Forceps on after-coming head	23	2	8	36	5	14

to section. The presence of any of the usual indications for cesarean section will justify the operation. With the tendency, too apparent in this country, to use cesarean section as a solution for all obstetric problems, its selection for the management of breech position should be carefully considered. A slightly greater latitude may be permitted in the cases of older primiparas but even here the mere fact of age does not outweigh all else. In our experience in all types of labor, our elderly primiparas have very little more trouble than our younger patients. Cesarean section should not be immediately decided upon merely because a primipara, whose infant lies in a breech position, happens to be a little older than the average. Table IX indicates the indications which caused the selection of abdominal delivery. Disproportion accounted for more than half the cases. Cesarean section occupies a definite place in the management of breech presentation, especially in primiparas, but should be reserved for those cases in which an adequate indication exists.

TABLE IX. CESAREAN SECTION

Disproportion	18
Toxemia	3
Recent fracture of pelvis	1
Placenta previa	2
Pulmonary tuberculosis	1
Repeat	3
Fibroids (Porro)	1
Heart	2
Indefinite	3
	34

A series of breech cases could scarcely be managed without some complications. These are indicated in Table X. Prolapsed cord occurs more easily in the presence of a breech presentation. There were

4 in this series, only one child being lost. If dilatation is complete, and the child is alive, immediate delivery is indicated. Of the 30 cases in which labor was induced the bag was used only twice. Our use of the bag is sharply limited to some cases of placenta previa, an occasional case of premature detachment, and cases of toxemia in which a necessity for prompt response exists. Our results with the Watson method of induction, and lately with the rupture of the membranes in selected cases, have been so satisfactory that we have had little inclination to make use of metreurysis.

TABLE X. COMPLICATIONS

		DEATHS
Prolapsed cord	4	1
Induced	30	4
Third degree tear	4	0
Thrombophlebitis	1	0
Polyhydramnios	3	3
Postpartum hemorrhage	10	2
Uterus packed 8		
Toxemia	6	4
Broken humerus	3	0
Broken clavicle	3	1
Injured arm	1	0
Craniotomy; hydrocephalus	1	0
Ablatio	1	1
Fibroids	2	1

The four third-degree tears which were recorded were repaired at once and in all four cases a satisfactory result was obtained.

In 11 cases there was postpartum bleeding. In 8 of these packing was used.

In difficult breech extractions it is sometimes difficult to avoid injury to the child. In 3 cases the humerus was fractured and in 3 others the clavicle. In one other case a slight Erb's palsy occurred which was followed by recovery. In cases in which it is difficult to bring down the arm a fracture of the humerus may occur. It is far better for the infant to suffer a fracture of the humerus than to have an injury of the musculo-spiral nerve or of the brachial plexus.

Injuries to the nerves of the upper extremity heal slowly and some loss of function may be permanent while injuries to the humerus heal rapidly. If a tiny wire splint is at once put on, an excellent result is usually attained. In our cases it has been impossible a few months later to tell which was the injured arm. We are indebted to our surgical colleagues for their help with these cases. The results in the cases of fracture of the clavicle were equally satisfactory. Prompt recognition is more important in bony injuries of the infant in order that necessary correction of possible deformity may be done at once. If any doubt as to the presence of bone injury exists, roentgenographic examination should be done.

In one case craniotomy of the after-coming hydrocephalic head was done. This was preceded by tapping of the distended cranium by a trocar passed through the occipital bone close to the spine. No attempt should ever be made to deliver a hydrocephalic infant by the breech without lessening the bulk of the head. If, after this, delivery presents any difficulty craniotomy should follow.

CONCLUSIONS

1. External version should be done if possible by the use of moderate force.

2. Conservatism, operative intervention being withheld until an indication develops, is the wisest course.

3. The mortality rate is smallest in infants weighing five pounds or more.

4. The mortality of breech delivery at term in skilful hands should be less than 10 per cent.

636 CHURCH STREET

PROLONGATION OF PREGNANCY IN THE RABBIT BY THE INJECTION OF PROGESTERONE*

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THE onset of parturition in many animals is preceded by regression of the corpus luteum and in some, such as the rat, mouse, and rabbit, removal of the corpora lutea is followed either by resorption or abortion of the embryos. In others such as the guinea pig (Herrick, 1928; Courrier, Kehl and Raynaud, 1929) and cat (Courrier and Gros, 1935), it is possible to remove both ovaries during the latter part of pregnancy without interfering with the progress of gestation in any way. The human being appears to belong to the latter group, since there are cases reported (Ask-Upmark, 1926) in which both ovaries were removed during the latter part without producing miscarriage. In the early part of pregnancy abortion usually follows removal of the corpus luteum (DeLee, 1916; Ochsner, 1920; Mackenzie, 1922). However, Pratt (1927) has reported two cases in which the corpus appears to have been removed at the very beginning of pregnancy (before a menstrual period had been missed) without abortion. In the human being and in those animals where castration can be performed without interrupting pregnancy, it would appear that the corpora could have no relation to the

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onset of parturition, but it is quite possible that in them the placenta may elaborate the same hormones as are produced by the ovaries of those in which the corpora are necessary to the end of pregnancy. In fact, there is some evidence that this may be so since in the castrated pregnant guinea pig the injection of estrin is not followed by an estrous response in the vaginal smear, the same inhibition being obtained as is obtained in the nonpregnant animal only when active corpora lutea are present (Courrier, Kehl and Raynaud, 1929). From this experiment it is assumed that the placenta elaborates an estrin-inhibiting substance. This may or may not be progestin but highly purified progestin-containing extracts of the corpus luteum are known to contain an estrin-inhibiting substance (Allen and Meyer, 1935). Recently numerous workers have reported the presence of progestin in human placentas (Adler, de Fremery, and Tausk, 1934; McGinty, McCullough and Wolter, 1936; Ehrhardt and Fischer-Wasels, 1936; Mazer and Goldstein, 1932; Smith and Kennard, 1936). Consequently it is not illogical to suppose that the onset of parturition may be due in part to waning of the corpus luteum or to lowering of the progestin level.

If parturition be due in part to waning of the corpus luteum, or to lowering of the amount of progestin present, then appropriate corpus luteum extracts administered just before the onset of parturition should delay parturition.

The first successful experiments designed to test this supposition were carried out by Nelson, Pfiffner, and Haterius (1930). They found that the injection of a methyl alcohol extract of pigs' corpora lutea (doses equivalent to 10 gm. fresh tissue per day) into pregnant rats beginning on the fifteenth to seventeenth day of pregnancy caused a delay of parturition amounting to about two days in most instances. Miklos (1930) obtained essentially the same results also in rats using an alcohol-ether extract of the corpus luteum. At about the same time Allen and Corner (1930) found that pregnancy could be maintained to term by injection of progestin in rabbits castrated the day after mating. Two of the animals reported by them actually failed to deliver at the usual time and delivery was accomplished by cesarean section on the thirty-fourth and thirty-sixth days. In both cases the fetuses were dead, but from their size it was apparent that some of them had survived to term, but in the presence of continued injection of progestin, delivery had failed to occur. Mandelstamm and Tachaikowsky (1932) found that a single injection of 1 c.c. of corpus luteum extract (cow) on the fifteenth to twentieth day of pregnancy in the mouse caused a delay of from four to ten days in 10 out of 12 animals. The manner of conducting the experiments was such that the exact amount of delay in each animal could not be stated, but the results are significant nevertheless. They also state that the period of delivery was prolonged and that the fetuses were of excessive size. Courrier and Kehl (1933) in a single case (rabbit) found that the injection of progestin from the twenty-second to thirty-fifth day of pregnancy, the rabbit having been castrated on the twenty-second day, maintained the pregnancy and prevented the onset of labor and at the termination of injections autopsy showed all the fetuses to be fully developed but dead. More recently Portman (1934) has found that the administration of large doses of corpus luteum extracts (up to 6 Rb.U. per day) greatly prolonged the period of gestation in rabbits, in some in-

stances doubling it. However, the fetuses did not continue to grow indefinitely, since they were always macerated when autopsy was performed at the conclusion of the experiment.

Interference with parturition was accomplished in each case by these workers with extracts either known to contain progestin or presumed to contain progestin because of the method of preparation. It is more than probable that they also contained estrin since these researches were carried out before either estrin-free progestin or progesterone were available. This fact makes it necessary to repeat the observations with progesterone before it can be said with surety that the inhibition of parturition obtained was due to the progestin injected, especially since we (Allen and Heckel, 1936) have found that the injection of estrin during the latter part of pseudopregnancy in the rabbit causes the corpora lutea to persist in a functional state.*

EXPERIMENTAL

The following experiments were carried out to ascertain whether or not progesterone would cause inhibition of parturition in rabbits. The number of animals is necessarily small because of the small amount of pure progesterone available and the large amount required for each animal, but they seem adequate to establish that it does markedly interfere with the onset of parturition. Both natural and synthetic progesterone were used. The natural hormone was prepared from sows' ovaries by the method of Allen and Goetsch (1936). The α form alone and mixtures of α and β forms were used. The synthetic hormone used was of the α form and was donated by E. Merck, Darmstadt. One milligram of crystalline hormone is equivalent to one Corner-Allen rabbit unit and to one international unit.

Virgin does were mated and then injected with various amounts of progesterone, injections beginning on the twentieth, twenty-fifth, or twenty-eighth day of gestation and being continued either until parturition had occurred or until it had been significantly delayed beyond the usual time for delivery (i.e., thirty-two days). The results are set forth in Table I. In cases in which 1.0 mg. or less was given per day beginning on the twenty-fifth day normal parturition occurred at the usual time (9, 10, 11, 63, 64, 65). When 1.5 mg. or 2.0 mg. per day was given, parturition was significantly delayed in nine out of ten animals and in one for as long as forty-five days. The mechanism of parturition was also disturbed in that the duration was considerably prolonged. In some cases a normal fetus was delivered at about the usual time and then at some later time postmature fetuses were expelled. Rabbit 21, for example, delivered one normal fetus and two dead ones on the thirty-fourth day and three dead ones early on the thirty-fifth; Rabbit 23 delivered a living fetus of normal size on the thirty-third day and three dead postmature fetuses on the thirty-fifth day. This is in direct contrast to a normal delivery where only an

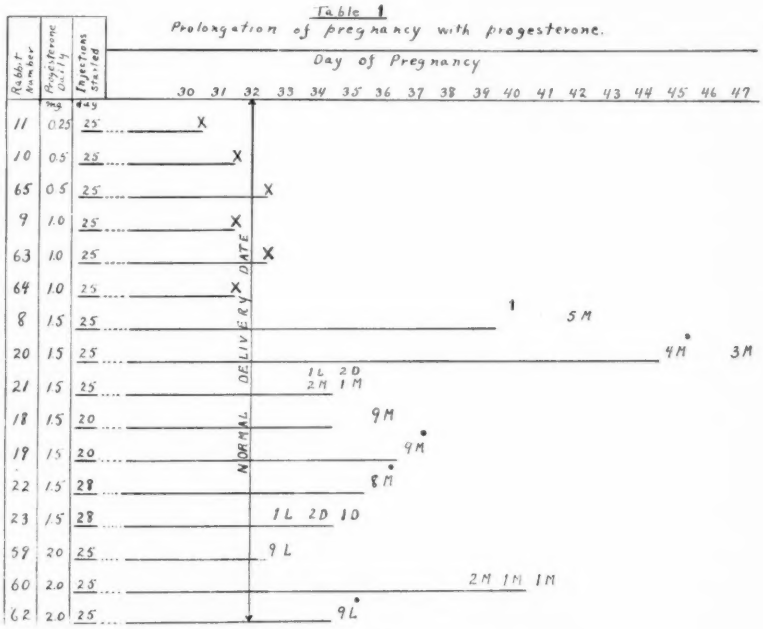
*Since this paper was presented for publication, experiments on the rabbit in which pregnancy was prolonged by injection of progesterone have been reported (Koff, A. K., and Davis, M. E.: AM. J. OBST. & GYNEC. 34: 26, 1937). By the injection of estrin in the rabbit, we have succeeded in prolonging the life of the corpus luteum of pregnancy as well as that of pseudopregnancy. Parturition is delayed when the corpora lutea are so maintained.

hour or so at most elapses between delivery of the first and the last fetus. It is also of note that in some animals delivery of dead fetuses occurred despite the continuation of injections. Rabbit 60 delivered two dead fetuses on the thirty-ninth day, one on the fortieth, and one on the forty-first day, injections being continued through the fortieth day. In cases where injections were stopped before delivery had taken place (18, 19, 20) delivery began within twenty-four to forty-eight hours. One animal in which postmaturity was very obvious by palpation (22) was delivered by cesarean section on the thirty-sixth day of 8 dead well-furred fetuses. The crown-rump length of these varied from 90 to 130 mm., indicating that they had survived for at least a day or two after the usual time of birth.

In practically all cases in which parturition occurred after the thirty-fourth day, postmaturity was apparent as judged by the size of the skeleton and amount of hair present, even though the fetuses at birth were not of excessive weight because of maceration.

Table 1

Prolongation of pregnancy with progesterone.



X, Spontaneous delivery of normal fetuses.

1 L, 2 D, 8 M, etc., one living, two dead, eight macerated, etc.

●, Young removed either by cesarean section or by autopsy. All others born spontaneously.

†, Exploratory laparotomy.

Solid black lines indicate period of injections.

1 mg. progesterone = 1 Corner-Allen unit = International unit.

The cause of death of the fetuses at about the thirty-fifth day was not always apparent. Rabbit 22, which was delivered by cesarean section of dead fetuses showing only very early maceration of the abdominal skin, had placentas some of which were still attached to the uterus. Another animal (20) was subjected to laparotomy on the forty-fifth day and one horn removed. The fetuses were large but badly macerated, the placentas all having been separated for a considerable length of time. The uterine wall in some areas appeared infarcted and section through such areas showed actual necrosis of the muscle presumably from pressure of the large, bony fetuses.

Observations were made on the mammary glands of all animals. In each case lactation began between the twenty-fifth and twenty-eighth day of pregnancy, as it normally does in rabbits of our colony, even though injections were begun as early as the twentieth day. At the thirty-second day the mammary glands were as well developed as those of untreated pregnant animals at term and copious amounts of milk could be expressed from the nipples. In those animals in which parturition was greatly delayed (8, 20, 60), the mammary glands slowly regressed even though milk could be readily expressed from the nipples.

Several animals were autopsied at the conclusion of the experiments and sections made of the ovaries to see if there was any effect on the corpora lutea but in none was there any evidence that their life had been prolonged. All were markedly degenerate microscopically and in gross they could hardly be recognized.

DISCUSSION

These experiments show that progesterone prepared either from pigs' ovaries or synthetically from stigmasterol delays the onset of parturition in most instances in rabbits if an adequate amount is given. The results for the most part are of the same type as those obtained by Snyder (1934) who introduced new lutein tissue into the ovaries of pregnant rabbits at about the twenty-fifth day by the intravenous injection of gonadotropic hormone. His thorough-going studies showed in a convincing manner that the presence of new lutein tissue at the time of expected parturition effectively prolonged the period of gestation to about forty days in most cases, although the fetuses appeared to live to only about the thirty-fifth day. The fact that our results with progesterone are similar to those of Snyder makes it apparent that the new corpora accomplished the delay obtained in his experiments by virtue of the progestin produced.

The results have considerable bearing on the rôle which progestin plays during pregnancy in the rabbit. Many experiments show that it is indispensable early in pregnancy, and in the light of these experiments, it is probable that it is required for nearly the entire span of gestation. Castration prior to the twentieth day results in resorption of the embryos and after the twentieth day in premature delivery (Hammond, p. 190; Courrier, Kehl and Raynaud, 1929). It is probable therefore that lowering of the progestin level in the body is responsible in part at least for the onset of labor, especially since raising the progestin level (as in the above experiments) prevents the onset of labor. The causes of the onset of labor in the human being may possibly be of similar nature even though the corpus luteum of pregnancy is not necessary throughout gestation because recent evidence makes it appear that the human placenta may produce considerable progestin.

The behavior of the mammary glands in these experiments is also interesting. It will be remembered that in the rabbit the alveolar system gradually grows during the first three weeks of pregnancy. Then during the next few days the alveolae begin to secret, the glands become

very thick, and beginning between the twenty-fifth and twenty-eighth day large amounts of milk can be expressed from the nipples, the glands being at this time indistinguishable from those obtained at the time of parturition on the thirty-second day. The actual production of milk is probably due to the secretion of a lactogenic hormone by the pituitary, but the hormonal factors precipitating the release of this hormone are not fully understood. In these experiments the injection of quantities of progesterone adequate to interfere with the onset of labor, appeared to have no effect on the secretion of milk. In two animals (18, 19) the injections were begun on the twentieth day, but this did not prevent the appearance of milk at the usual time. However, in animals in which the fetuses were retained for a long time (8, 20) the mammary glands receded markedly after about the thirty-fifth day, even though milk could be expressed from the nipples at all times after the twenty-fifth day. The reason for this has not been determined, but it may be due to the fact that the placentas become separated and nonfunctional shortly after the death of the postmature fetuses.

The amount of progesterone necessary to prevent or delay the onset of parturition appears to be large (1.5 mg. per day) when compared to the amount necessary to produce progestational proliferation in the recently castrated rabbit. It requires only 0.2 mg. (0.2 I.U.) per day for five days to accomplish this (Wintersteiner and Allen, 1934), but such a quantity is apparently not physiologic, because Allen and Corner (1930) found it to be inadequate to maintain pregnancy to term, about 1.0 unit per day (equal to 1 mg. of progesterone) for this purpose being necessary. Recently Makepeace, Corner, and Allen (1936) have found it requires 1 mg. per day for five days to desensitize the rabbit uterus to pituitrin (in vitro), and Allen and Heckel (1936) have shown that it requires 1.5 mg. per day after the fifth day to maintain pregnancy changes for an additional five days. These observations make it evident that in the rabbit large doses are necessary to bring about conditions in the uterus optimum for normal implantation. In view of this, it is not surprising that equally large doses are necessary to interfere with the onset of parturition. These doses are huge when compared to those being recommended for clinical use at the present time, but it must be openly admitted that the entire question of dose for human needs is unsettled. However, in clinical cases in which progesterone should theoretically give benefit but does not, it should not be condemned until a dose has been given which is more in accord with animal experimentation than those already in use.

CONCLUSIONS

The subcutaneous injection of 1.5 mg. (1.5 I.U.) or more of progesterone per day in rabbits, beginning as late as the twenty-eighth day of gestation, effectively delays parturition in most cases and may pre-

vent it altogether. The fetuses become postmature, but do not live longer than the thirty-fifth day in utero. In many instances parturition itself is quite abnormal, the time required for delivery of the entire litter being several days.

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QUININE IODOBISMUTHATE IN THE TREATMENT OF SYPHILIS COMPLICATING PREGNANCY

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NUMEROUS studies have shown that syphilitic pregnant women if adequately treated, will be delivered of normal babies in a high percentage of instances. Arsenical therapy has thus far proved most efficacious in continuing the pregnancy to a successful termination. Bismuth as an adjuvant following the course of arsenical treatment has also been widely recommended. The treatment of syphilis in pregnancy with bismuth alone has received but scant attention. This method of therapy was strongly recommended by Cabouat[2] in 1923, only one year after the introduction of bismuth treatment for syphilis.

A review of the available literature discloses relatively few reports, chiefly from French clinics in which bismuth alone was employed in the treatment of syphilitic pregnant women. Cabouat[2] reported favorably on the treatment of four pregnancies with trepol (tartrobismuthate of Na and K), neotrepol, and quiniobismuth, in which four full-term living babies resulted, one of which was syphilitic. Le Louer and Galliot[7] after treating 13 women, 10 by intravenous injection of colloidal bismuth, and 3 by intramuscular injection of the hydroxide of bismuth, conclude that the results compared well with those noted with arsenical

therapy. Bizard and Jolivet,[1] however, were confident that arsphenamine therapy would have prevented the disastrous results which they obtained following the use of quinine iodo-bismuthate in two instances in which it was employed: in one, in which 20 injections were given to the mother, the child developed syphilides over the entire body and died two months after delivery, while in the other a miscarriage occurred after more than 10 treatments had been given. Galliot[5] reported a group of 27 patients who received intramuscular injections of bismuth hydroxide, resulting in 85 per cent live births, while of 29 arsphenamine treated patients in the same clinic, 89 per cent live births occurred. Pouget[11] on the basis of 3 fetal mortalities during bismuth therapy, did not consider it as suitable in the treatment of syphilis complicating pregnancy. Zakon[15] has reported a series of 21 pregnant women treated with bismuth salicylate, while 5 patients received bismuth and neoarsphenamine. Twenty-six full-term clinically healthy children, 25 of whom were serologically negative, were reported for the group. Six or more injections were given in all but 5 instances.

Notwithstanding the fact that bismuth therapy of syphilis in pregnancy has been limited, its use has been recommended by a number of eminent syphilologists, especially on the strength of its innocuousness, its high renal tolerance, its relative freedom from reaction and ease of administration. Schamberg and Wright[13] conclude that: "bismuth may be successfully and safely given during the period of gestation and the period of lactation. Active lesions disappear rapidly, and in old cases, if treatment is begun early and continued throughout the period of gestation, the pregnancy comes to full term."

In the present report a study is made of 34 pregnant syphilitic women treated solely with bismuth, in the form of intramuscular injections of quinine iodobismuthate. The drug is a red precipitate suspended in oil, and, according to Levaditi,[8] has a bismuth content of 23.85 per cent. Quinine iodobismuthate was introduced by Fournier and Gernot in 1921 and 1922. It received early recommendation by Cabouat[2] for the treatment of syphilis in pregnancy, for which it was also used by Bizard and Jolivet.[1]

In a more recent report Oliver and Crawford[9] give results indicating that quinine iodobismuthate is superior to bismuth salicylate in spite of its lower bismuth content. They suggest that the quinine and iodide may play a rôle as well as the ionic state of the bismuth.

MATERIAL AND METHODS

A total of 34 consecutively registered syphilitic pregnant women received antisyphilitic treatment with quinine iodobismuthate in the form of intramuscular injection of 2 c.c. of a 10 per cent suspension in oil. Each cubic centimeter of the drug contains approximately 30 mg. of metallic bismuth (N. N. R.).

All of the women who received treatment had positive Wassermann and Kahn reactions. Twenty-eight were colored and 5 were white patients. A history of antisyphilitic treatment in previous pregnancies was noted in only 4 women of this group; it was also observed, however,

that no fetal mortalities resulted from these pregnancies. Previous stillbirths or miscarriages were noted in 8 or one-third of the 24 multigravidas of this series.

Antisyphilitic treatment was given at weekly intervals from the time of registration until the termination of the pregnancy, except in those instances in which the patient did not return regularly for treatment. A total of 205 intramuscular injections of quinine iodobismuthate were given to 34 pregnant patients. Twenty women received six or more treatments. Only 12 patients, however, started treatment prior to the sixth lunar month of gestation. The largest number of injections given were 17, which were administered to two patients.

RESULTS OF TREATMENT

The outcome of the pregnancy among the 34 pregnant syphilitic women who were treated with quinine iodobismuthate alone is given in Table I. It will be seen

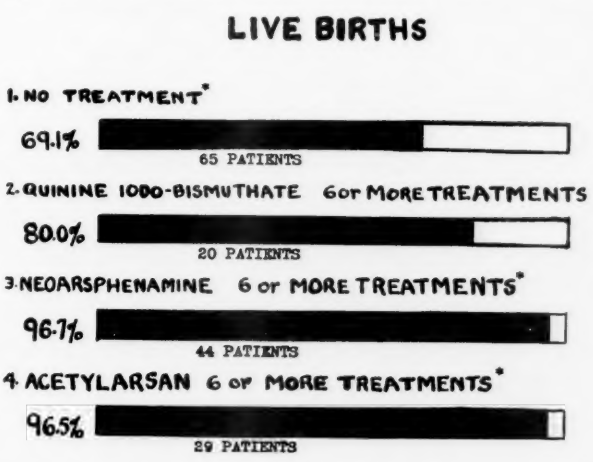

Chart 1.—Comparative efficacy of quinine iodobismuthate, neoarsphenamine, and acetylarsan.

that 6 (17.6 per cent) of the patients were delivered of stillborn babies. The remaining 28 women (82.4 per cent) had live births. Among the latter group one neonatal death occurred, while another child displayed evident signs of syphilis in the form of bullous skin lesions and "Snuffles" during the neonatal period.

Only 26 or 76.5 per cent of the total group were discharged with living apparently healthy children. Of the 12 cord blood Wassermann reactions taken among this group, 4 were positive, 6 were negative, and 2 were anticomplementary. It is the present concensus, however, that the result of the cord blood Wassermann reaction is of little significance; a positive result is an indication for further study of the baby, while a negative reaction does not eliminate the possibility of congenital syphilis.

Among a total of 20 women (Table I) who received 6 or more treatments with quinine iodobismuthate, 4 (20 per cent) had stillbirths; while among the 12 women who started treatment before the sixth lunar month, 3 (25 per cent) had stillbirths. In a previous study from this clinic, we[3] demonstrated that six or more treatments during pregnancy with neoarsphenamine or with acetylarsen insured

live births in more than 96 per cent of the pregnancies, while among the untreated mothers only 69.1 per cent had live babies (Chart 1).

An analysis of the six cases which resulted in stillbirths (Table II) indicates that syphilis was the only attributable cause of the fetal mortality in 5 instances, while in the sixth case in which there was a premature onset of labor in the seventh lunar month with a breech presentation followed by breech extraction, both syphilis and excessive birth pressure were given as possible causes of fetal death.

TABLE I. RESULTS OF TREATMENT WITH QUININE IODOBISMUTHATE

	ENTIRE GROUP	GROUP RECEIVING 6 OR MORE TREATMENTS	GROUP STARTING TREATMENT BEFORE SIXTH LUNAR MONTH
Pregnant women treated	34	20	12
Live births	28 or 82.4%	16 or 80%	9 or 75%
Stillbirths	6 or 17.6%	4 or 20%	3 or 25%
Miscarriages	None	None	None
Neonatal deaths	1 or 2.9%	None	1 or 8.3%
Babies living but clinically syphilitic	1 or 2.9%	None	None
Babies living and apparently healthy	26 or 76.5%	16 or 80%	8 or 66.7%

TABLE II. ANALYSIS OF FETAL AND NEONATAL MORTALITIES

OUTCOME OF PREGNANCY	ATTRIBUTABLE CAUSE OF DEATH	LUNAR MONTH TREATMENT STARTED	NO. OF TREATMENTS
Stillborn. Premature. Seventh lunar month.	Syphilis	4th	8
Stillborn. Premature. Seventh lunar month.	Syphilis. Excessive birth pressure?	5th	8
Stillborn. Full term. Macerated.	Syphilis	8th	4
Stillborn. Full term. Macerated.	Syphilis	9th	2
Stillborn. Full term. Dead before onset of active labor?	Syphilis	4th	17
Stillborn. Full term. Dead before onset of active labor?	Syphilis	6th	6
Neonatal death. Premature. Seventh lunar month.	Syphilis? Prematurity?	5th	5

Of the 6 stillbirths, 2 were premature (seven lunar months), 2 were macerated when expelled at term, while in the other 2 indications of intrauterine fetal death were noted before the onset of active labor. It will also be noted that 4 of the 6 mothers who had stillbirths received 6 or more injections of quinine iodobismuthate.

The neonatal death recorded in Table II occurred in a child born prematurely at 7 lunar months, who was clinically syphilitic. The mother had received 5 treatments of quinine iodobismuthate starting in the fifth lunar month of gestation.

Reactions or toxic symptoms, immediate or remote, were not noted in any of the women treated with quinine iodobismuthate, nor were abortions or miscarriages induced. The injections with but few exceptions did not give rise to painful swellings. Abscesses did not occur in any instance.

DISCUSSION

Quinine iodobismuthate affords but little protection in successfully carrying a gestation to term as compared with women who received no treatment. In our hands it proved to be far inferior to neoarsphenamine and acetylarsan in similar groups of patients.

The results of Cabouat[2] and others indicate that treatment with bismuth, if started early in pregnancy, will offer adequate protection. This is frequently impossible in the ordinary clinic, where the majority of registrations occur in the last trimester. Further, it was noted that the results among patients who received more than 6 treatments with quinine iodobismuthate were no better than those obtained for the group as a whole. Early institution of treatment did not appear beneficial, a factor which is known to be of definite advantage in arsenical therapy.

It is probable that the failure of treatment in pregnancy by intramuscular injections of oil suspensions of bismuth alone can be attributed largely to its relatively slow absorption. In this respect the choice of quinine iodobismuthate was perhaps ill chosen for the present study in spite of its recommendation by early workers. As pointed out by Levaditi,[8] "taking into account its feeble bismuth content in comparison with other bismuth preparations, quinospirol is to be recommended especially for courses of consolidation rather than for a treatment of attack."

The investigation of Sollman, Cole and Henderson[14] indicates that bismuth preparations in oil suspension are absorbed less rapidly than those in oily solution, while the water soluble preparations are absorbed more rapidly than the latter. It has been demonstrated by Raiziss, Severac, and Moetsch[12] that the oil soluble compounds are only slightly more toxic than those in suspension, while those dissolved in water are considerably more toxic. It would seem that oil soluble preparations would be more suitable for the treatment of syphilis in pregnancy.

In addition to the question of absorption, the extent of placental transmission of bismuth is of practical importance in the protection of the fetus. The experimental work of Pack, Scharnagel, and Veal[10] in pregnant rabbits and cats has demonstrated that with the usual therapeutic doses the amount of bismuth transmitted through the placenta is practically nil. Although bismuth was demonstrated in the fetal kidneys after the administration of toxic doses, it was found that pathologic changes were not induced until the amount of bismuth introduced into the pregnant animal approached 60 times the therapeutic dose for human subjects. More recently a small but irregular elimination of bismuth in the human uterine secretion during the course of therapy has been demonstrated by Durel and Manin.[4]

The conflicting results of the clinical trial of bismuth preparations in pregnancy is evident from the review of the literature given below. The excellent results of treatment with bismuth salicylate, as reported by Zakon,[15] are not in agreement with the results of the present study; in view of the clinical experience of Oliver and Crawford[9] indicating that quinine iodobismuthate is superior to bismuth salicylate in the treatment of syphilis.

Since early and energetic treatment of syphilis in pregnancy may mean the difference between a living and a dead baby, intravenous arsenical therapy is to be desired in every case except where definitely contraindicated. In the usual dosage the arsenicals are tolerated as well, if not better, by the pregnant woman, than by the nongravid syphilitic patient.

When used in conjunction with the arsenicals, it cannot be denied that bismuth is of value in the treatment of syphilis in pregnancy. After a series of arsenical treatments it affords a safe and convenient method of continuing antisyphilitic treatment while the patient is given a rest before further arsenical administration. It deserves, especially, to be used simultaneously with arsenicals in syphilitic women who present themselves in the last weeks of pregnancy.

Abortifacient effects due to bismuth, especially when combined with quinine, have been suggested as a contraindication by Bizard and Jolivet,[1] Juliusberg,[6] and by Pouget.[11] This belief has not received general confirmation by other workers using bismuth alone, or bismuth as part of mixed treatment. In the present study not a single abortion or miscarriage occurred in spite of the observation that treatment was started with quinine iodobismuthate prior to the fourteenth week in 3 instances, and earlier than the twenty-eighth week in 23 instances. That no pregnancy was terminated earlier than the seventh lunar month may well be taken to indicate some protective influence exerted by treatment with this drug.

SUMMARY

1. A group of 34 pregnant syphilitic women were treated with quinine iodobismuthate by the intramuscular injection of 2 c.c. of a 10 per cent suspension in oil once a week.

2. Only 26 or 76.5 per cent of the total group were discharged with living apparently healthy children. Six babies were stillborn, one died neonatally, while another developed evident signs of syphilis.

3. Among 20 women who received 6 or more treatments, 4 (20 per cent) had stillbirths, while among 12 women in whom treatment was started before the sixth lunar month, 3 (25 per cent) had stillbirths.

4. From a comparison with other groups of syphilitic pregnant women observed in this clinic it is concluded that quinine iodobismuthate afforded little protection to the pregnancy, and was markedly inferior to arsenical therapy.

Acknowledgment: The authors are indebted to Dr. P. Brooke Bland and Dr. Norris Vaux, whose cooperation has made this study possible; and for their constant interest and aid.

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248 South Twenty-First Street

SHORT-WAVE THERAPY IN GYNECOLOGY AND OBSTETRICS

Experiences With One Hundred Twenty Cases

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THE application and use of oscillatory electrical current of various frequencies in the different fields of medicine and surgery has been an extremely interesting excursion to watch. That it has been of value is attested by its steadily increasing application and various attempts to augment the scope of the differing physical procedures already in use. Within recent years waves of very high frequency, variously known as short wave, ultra-short wave, radiothermy, etc., have largely supplanted the interest in diathermy. It is rather obvious from the literature that some of the over-enthusiastic operators have confused therapeutic claims with indisputable results, but in spite of this rather human trait it is important that we evaluate this convenient and seeming practical method for producing deep-seated heat in any part of the body. Although claims have been made, notably by foreign writers, that the short-wave current produces physiologic effects other than heat, it has been difficult, in fact essentially impossible, to prove such statements. Therefore, while one may not forthwith dismiss the possibility

that other effects are produced by such treatment, it is safest to assume that beneficial results are derived from the heat created, and solely from the heat.

An understanding of the basic principles underlying the application of this form of therapy is important in considering the manner in which the effects are produced. The temperature rise is caused by the flow of short-wave current within the body. The wave in its passage, if it be an alternating or oscillating current, dissipates energy and produces heat. This can be explained by the manner of the electrical or molecular disturbance which takes place under the influence of the impressed voltage. As the current flows, the molecules are distorted, first in one direction and then the other; in effect, there is a vibration of these molecules, the vibratory rate being at the same frequency as the oscillating rate of the applied current and the intermolecular friction caused by this motion produces heat in the mass of tissues.

With ordinary diathermy current, the vibrations take place at the rate of only 600,000 to 1,000,000 per second, and because of this relatively low oscillatory rate, direct metallic skin contacts are required to introduce the energy into the body.

But when currents of extremely high frequencies are applied, such as those of short-wave length, the displacement of vibratory rate of the molecules will run from 12½ to 30 million per second. Because of this very high frequency, we are able to introduce the current into the body without direct metallic contact.

In actual application of short-wave currents, there are two methods of introducing the energy into the body. One is commonly known as the condenser field method (pads) and the other as the magnetic field (inductance cable).

With the condenser field method, the metallic element in the insulated applicator pads is separated from the patient's skin by rubber or other insulation, and these metal plates together with the patient's skin form a condenser of small capacity. This small capacity would offer a tremendous impedance (or resistance) to the relatively long-wave lengths, such as are used in medical diathermy and such current would not flow. However, when the frequency is high enough (10 million or more oscillations per second) these capacities or condensers offer a negligible impedance, and the current flows freely from the metal plates through the insulating materials to the patient's skin, then through the intervening tissues, and out through the other condenser pads. Heat is created in the intervening tissue structures through the molecular activities engendered, as previously described.

If we remember that the human body consists of a multiplicity of cells of varying electrical characteristics, it may be reasonably considered to form many minute condensers, often with resistances in series

and in parallel. Thus, when dealing with a short-wave current, one may assume that once introduced into the body, the current will divide itself between resistive and capacitative paths and that the heat so created may be partly attributed to combinations of effects, viz., first a resistive heating in the resistive paths plus heating due to losses in many minute condensers.

We can visualize further freest passage of these currents through paths of low resistance, such as muscle, the vascular organs of the viscera, and the immediate subcutaneous tissues with their free peripheral circulation, and we can visualize that the current will tend to jump around or over the highly resistive tissues, such as bone, cartilage, fascia, etc., due to the condenser effect induced by these semi-insulators.

With the assumption that the freest current flow will take place in the good conductors (that is, the highly vascular moist tissues, the blood stream, etc.), whereas lesser current will flow in the semi-insulating tissues, we may presume that currents of very short-wave length (or very high frequency) will tend to seek out and flow freest through the most conductive structures. This may explain the apparent localization and beneficial effect on infected areas where edema or high aqueous content would create a low resistance, highly conductive path.

As previously stated, with the condenser field method, the current must flow from one applicator through all intervening structures and out through the second applicator. This is somewhat at variance with the second method of introducing short-wave currents into the body, viz., the so-called magnetic field or inductance cable applicator.

With the cable, heating is effected not by current passing through the body, but rather by the flow of secondary current induced in the body as the current flows in the coiled-up cable near or on the mass of tissue being treated.

Current from the generator is conducted through a flexible, heavily insulated cable which is either wound around the part to be treated or placed in the form of a flat "pancake" over the tissue where heat is desired.

Within the coiled cable, an alternating magnetic flux is set up by passage of the current. When a conductive body is placed in or near the coil, an electromagnetic force is induced which causes eddy currents of the same frequency as the current in the cable to flow in conductive parts of the body mass.

These eddy currents do not have to flow *through* intervening structures, but rather will they circulate within the various tissues. The greatest current will tend to flow and consequently greatest heat will be produced in the more conductive structures, without unduly heating the skin. Because of its flexibility and ease of application, the cable

is found extremely convenient in treating irregular contours of the body such as a shoulder, neck, joints, etc., where physical structure makes application of the condenser pads difficult.

These two methods are described because one will be found more convenient for certain applications. It is doubtful if there is any therapeutic difference in the effects produced.

While I have spoken of the tendency to create greatest heat in the tissues of greatest conductivity, it is doubtful if practical differential heating can be accomplished and controlled due to the temperature equalizing effects in the tissues of heat conductivity and blood flow. In practice, one must assume that all body structures, lying between the plates of the condenser applicators or within the field of the inductance cable, must have temperature elevations of varying degree and duration.

Our interest in the possibilities of short-wave therapy in obstetrics and gynecology was aroused by its presumed ability to produce heat for conditions and in locations otherwise inaccessible to it in the usual form. In the several conditions herein reported it had long been felt that if heat could be applied adequately, safely, and easily, much benefit would be derived. It was decided to use short-wave therapy in such conditions as might conceivably benefit from tissue heat and the physiologic tissue changes resulting therefrom, and a course of therapy planned. All of the treatments were given on patients in the hospital and given under careful supervision and observation. Accurate records were kept, not only of the time intervals, the number of treatments, the obvious effect as determined from the clinical chart, and the eventual outcome, but also of the patient's response to this type of therapy so far as it concerned her subjective symptoms and most especially, pain relief. Many of the early treatments were given by one technician, although no highly trained operator is needed. The procedure was applied in different conditions encountered where application of heat might be expected to arouse local or general beneficial response. Nothing was expected over and above the ability of the modality to produce heat in the area treated.

RESULTS

Sixty-four patients who presented as the outstanding symptom infected and foul lochia, were observed and treated with short-wave therapy. Many of these were accompanied by tenderness of the uterus, and several were complicated by very high temperature and pelvic pain. Upon instituting short-wave therapy, it was noted that there was a marked increase in the lochia after the first or second treatment, subsequent to which there was a rapid or gradual change to normal. Where pelvic pain and uterine tenderness had been an outstanding symptom, the patient invariably reported symptomatic improvement. The foul lochia cleared in all but 4 of these 64, and in 2 cases the patient's condition progressed to general sepsis.

Seven of 8 cases of subinvolution of the uterus responded promptly to therapy, although 3 patients had been treated by the usual oxytocics without response. In

TABULATION OF CASES

DIAGNOSIS	NO. CASES	DAYS TREATED		AVERAGE NO. DAYS	NO. TREATMENTS		AVERAGE NO. TREAT.	NO. TREATMENTS BEFORE ANY IMPROVEMENT		AVERAGE NO. BEFORE ANY IMPROVEMENT	RESULTS
		MIN.	MAX.		MIN.	MAX.		MIN.	MAX.		
Foul lochia, endo- and myometritis	64	2	12	5.3	5	30	9.6	4	14	6.8	60 Satisfactory 4 No change
Subinvolution of uterus	8	1	4	2.1	2	12	4.7	2	4	2.8	7 Favorable 1 Dilatation and curettage for retained secundines
Dysmenorrhea	10	1	1	1.0	1	2	1.4	1	2	1.4	6 Complete relief 4 None
Myalgias	16	1	6	2.8	1	8	3.9	1	8	3.0	14 Marked to complete relief 2 No relief
Breast abscess	12	1	5	3.6	3	15	6.6	3	10	5.4	7 Incised and drained 2 Spontaneous drainage 3 Cleared without incision
Phlebitis	10	9	28	14.2	16	36	21.4	1	19	7.2	9 Relieved completely 1 Improved

one case there was a marked increase in bleeding amounting to hemorrhage, and this patient was subsequently found to have a large intrauterine piece of retained placenta.

In 10 cases of dysmenorrhea treated, the results were less startling. Mindful of the many possible causes of dysmenorrhea, it is not surprising that 4 failed completely of relief. None of these 4 showed gross pelvic abnormalities to account for the dysmenorrhea. In the 6 patients who had complete relief, the pain recurred in 4 at subsequent menstrual periods. However, in 3 of these 4 repetition of the treatment again effected temporary relief.

The most constant results were obtained in myalgias of the extremities, back, and neck, where the response was early and permanent and with a minimum number of treatments. These were in keeping with our knowledge of the response of myalgias of various forms to any type of heat therapy, wherein the amelioration of pain and tenderness depends largely upon heat effects of counterirritants, plasters, poultices, and similar forms of tissue heating applications.

The 12 cases of breast abscess recorded gave better results than the figures indicate. Seven of these came to incision and drainage, but the subsequent course could be fairly described as being less painful and associated with more rapid convalescence than one would ordinarily expect. Two cases ruptured before incision was made during the course of treatment, and in each instance there was a rapid subsidence in the infective reaction in the breast itself. In three instances inflammatory conditions in the breast, diagnosed clinically as breast abscess and showing marked tenderness, redness, induration of tissue, pitting edema of the overlying skin, and systemic reaction in the form of fever and headache, subsided after persisting treatment without incision and drainage and gave no subsequent trouble.

Ten patients with phlebitis were treated and clinical cure effected in 9 of these 10. The average period of disability was not much shorter than with other forms of therapy, but the relief to the patient came earlier and was more definite and lasting than those observed and treated by other methods. Analgesics were dispensed with in nearly all cases after the third treatment.

There was no increase in systemic temperature in any of the cases treated at the completion of any given treatment. Where any change in temperature was noted, it was in a downward direction.

COMMENT

The clinical impressions gleaned from this group of cases indicate that short-wave therapy is of real service in gynecology and obstetrics. An understanding of the patient and her condition, complemented by thorough appreciation of the physiologic changes induced by such treatment, is imperative before instituting therapy. The prompt and favorable response of the patient and the amelioration of pain in such diverse conditions as parametritis, myalgia, and phlebitis are too definite to be lightly dismissed. There were no untoward reactions nor complications due to the use of short-wave therapy in any of the cases observed, including those in which no benefit was obtained. The meteor length of the short wave used seemed to be of no clinical importance. There was no change in systemic temperature. Frequently, there was a marked improvement in the patient's general condition which was difficult to ascribe to the treatment; the intervention of psychic factors frequently plays a rôle in therapy of this form.

The ease of application is notable. In all forms of pelvic pathology requiring treatment, the transabdominal application of pads was used. Many of the myalgias may be treated by the condenser field method using pads but in general are more conveniently managed with the inductive cable applicator. Both methods were used in this series. The reaction of the patient to this form of therapy is extremely interesting. Although at first a few were fearful, the majority were tremendously interested and almost invariably liked the treatment. The early pain relief undoubtedly accounted for the patients' favorable mental response.

The brief treatment time, which averages but fifteen minutes, the ease and safety of application offer advantages not to be found in other forms of heat therapy. No specially trained personnel is needed. There is scant danger of contact or spark burns with pads transmitting wave lengths under 20 meters, although accumulations of perspiration drops under condenser-field pads is guarded against by interposing an absorptive cloth.

The treatment time averaged fifteen minutes, the frequency one to three times a day. Treatments were continued until relief seemed permanent or until it was felt that persistence in heat therapy was useless. Beneficial effects were noted in from two to seven treatments. Excepting phlebitis, those conditions responding favorably required five days or less for satisfactory completion of therapy.

SUMMARY AND CONCLUSIONS

1. The theory and principles of short-wave therapy are considered.
2. The practical results in 120 cases are recorded.
3. Rigid adherence to valid indications and careful recording of experiences is urged, to properly evaluate the worth of the modality.
4. For the present, the beneficial results obtained are credited to the deep heat created only. It is not a "cure-all."
5. From our experiences, we believe short-wave therapy an exceedingly important method of treating certain gynecologic, postpartum, and postoperative conditions. We regard it as a valuable adjunct to present therapy.

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Wood, J., Sabioncello, R., and Breiva, I.: Granulosa Cell Tumor of the Ovary. Bol. Soc. Chilena de obst. y ginec. (Buenos Aires) **2**: 129, 1937.

The authors review the literature and report a case of granulosa cell tumor of the ovary. The treatment was operation followed by radiotherapy. Two and one-half years later the patient is in good health.

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POSTPARTUM HYPERTENSION FOLLOWING A NORMAL PREGNANCY

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HYPERTENSION, observed at the routine examination six weeks postpartum, is not unusual, since it is frequently found in cases of nephritis, essential hypertension, or following certain toxemias of pregnancy. These increased pressures continue for a variable period of time, usually six to ten weeks, after which they return to normal, unless some degree of permanent kidney damage is present. On the other hand, postpartum hypertension after a perfectly normal pregnancy is an unusual condition and, up until the present time, it has been noted in the literature only once.

This condition was first called to our attention in 1934, when two patients presented themselves at the clinic in one afternoon. Several weeks later, I came across an article* dealing with the subject under discussion. After careful searching of the literature, no other reference was found. The purpose of this paper is to call attention to the existence of this finding, and to give the results of the investigation carried out, in an attempt to throw some light on its cause. The following statistics were obtained from the Out-patient Obstetrical Department of Touro Infirmary for the eleven month period from August 1, 1935 to July 1, 1936.

Incidence.—During the aforementioned period, 490 patients received the routine six weeks postpartum examination (279 white and 211 colored). Of this number, 23 cases, all colored, revealed postpartum hypertension after an apparently normal pregnancy. The incidence therefore is 1 in 21 or 4.6 per cent, as compared to Stout's reported incidence of 17.2 per cent. The latter's group, however, includes both white and colored patients, while as yet I have never seen a white woman display this phenomenon.

Age.—The age varied considerably, the youngest being seventeen years, the oldest, forty-two years, and the average, twenty-eight years. The group from twenty-one to thirty-one years comprised 56 per cent of the series.

Parity.—The series is composed of 4 primiparas (17.4 per cent) and 19 multiparas (82.6 per cent). Of the multiparas, there were:

Gravida 2—1	Gravida 5—2
Gravida 3—4	Gravida 6—2
Gravida 4—3	Gravida 7, 8, 9, 11, 12, 13, and 15—1 each

Stout's series consisted of 26.8 per cent primiparas and 73.2 per cent multiparas.

Period of Time Patients Were Observed During Prenatal Period.—When the patients in this series first enrolled in the prenatal clinic, 4 (17.3 per cent) were in the

*Stout, M. L.: Am. J. Obst. & Gynec. 27: 730, 1934.

first trimester of pregnancy, 14 (60.8 per cent) in the second, and 5 (21.7 per cent) in the third. The least number of prenatal visits a patient made was 3, and the greatest number, 16. The average number of visits made to the prenatal clinic was 9. Nineteen patients (82.6 per cent) made 6 to 16 visits.

Blood Pressure During Pregnancy.—On our service at Touro Infirmary, we consider a systolic pressure of 130 and over and a diastolic of 90 and over, as abnormal. Sixteen patients of the series neither during pregnancy nor labor exhibited an abnormal pressure at any time. The remaining 7 cases did go slightly above the normal mark occasionally, but due to the marked increase postpartum, these cases are added. An analysis of this latter group reveals:

CASE 136-967.—Enrolled when twelve weeks pregnant. Blood pressure 130/70; at second visit two weeks later it was 134/80; for the following nine to ten weeks her pressure ranged from $\frac{112\text{-}120}{70\text{-}80}$; when twenty-five weeks pregnant, her pressure was 140/80, after which it returned to normal with no treatment, and remained so, even through labor. At the postpartum examination, her pressure was 134/96.

CASE 25230.—Enrolled when about sixteen weeks pregnant. Blood pressure was entirely normal until patient was thirty-six weeks pregnant, at which time it rose to 120/94. One week later it was 134/94, the following week, 120/94, and the next week 112/80. Thirteen days later, she went into labor, the blood pressure rising to 148/90. At the postpartum examination, it was 160/146. This patient gave a history of having had hypertension four years previously, following a miscarriage.

CASE 139-142.—When this patient was twelve weeks pregnant, an electrocardiographic reading was done, and evidence of myocardial damage found. Diagnosis: Congenital heart disease (patent ductus arteriosus). The blood pressure at this time was 118/64. Maximum blood pressure during pregnancy was 134/84. (No other information available.) During labor, 140/80. Six weeks postpartum it was 176/110.

CASE 90419.—Enrolled when twenty-four weeks pregnant. Blood pressure normal until four weeks later, when it rose to 132/85. It remained abnormal for six weeks, the maximum reading being 136/88. For the remaining six weeks, the pressure varied from a low of 108/70 to a high of 128/84. No blood pressure reading was made during labor. At the postpartum examination the pressure was 180/110.

CASE 140-263.—Enrolled when thirty-five weeks pregnant. Blood pressure at this time was 114/60. The following week it was 130/80. She was given a salt-free diet and the succeeding two weekly readings showed the pressure to be 116/70 and 110/60. The pressure was not recorded during labor. At the postpartum examination it was 174/100.

CASE 90076.—Patient enrolled when twenty-six weeks pregnant. Pressure $\frac{110\text{-}120}{60\text{-}70}$ until six weeks later, when it rose to 140/82. The next three visits revealed pressures of 148/88, 138/66, and 120/90. The only form of treatment was a salt-poor diet. For the last four weeks of pregnancy, it rose to 160-94. At the postpartum examination it was 156/104.

CASE 106-619.—Patient enrolled when twenty-five weeks pregnant. Blood pressure ranged from $\frac{120\text{-}128}{78\text{-}88}$ until two days prior to onset of labor, when it rose to 128/90. The following day it was 134/90. No pressure reading was taken during labor. Six weeks postpartum, it was 170/110.

Postpartum Examination.—Hypertension: It was amazing to note the marked increase in pressure in some of the cases. All 23 patients in the series showed an

abnormal systolic pressure, the extremes being 134 and 200. Seven (30.4 per cent) were between 130 and 140; 15 (65.2 per cent) were between 140 and 180, and 1 (4.3 per cent) had a pressure of 200.

An abnormal diastolic pressure was found in 21 cases (91 per cent), ranging from 90 to 146. Eleven cases or 52.3 per cent were in the 90 to 100 group, 7 or 33.3 per cent in the group from 100 to 120, and 3 or 14.2 per cent ranging from 120 to 146.

It is interesting to note here that in three cases the pressure did not reach its maximum at six weeks. In Case 43589, the pressure at the postpartum examination was 136/92; four weeks later it had risen to 150/114, the rise being gradual and persistent. However, at the medical examination which was done forty-four weeks postpartum, the pressure was 118/80. Case 77739 showed a pressure of 162/80 six weeks postpartum; one week later it was 168/100, and the following week 154/110. Two weeks later (ten weeks postpartum) the pressure was 128/84 and it remained normal thereafter. She had received no treatment. Case 82348 had a blood pressure of 140/84 six weeks postpartum. One week later it was 142/90; the following week, 134/96. It returned to normal thirteen weeks postpartum.

Return of Blood Pressure to Normal: In most cases, a medical examination was not made until some time after delivery, so that a variable period of time intervened between the six weeks postpartum examination and that done in the medical clinic. For this reason, it is impossible to state exactly when the pressure returned to normal. Only in 8 cases was it definitely established that a normal pressure was finally attained during this study.

	BLOOD PRESSURE AT 6 WEEKS EXAM.
2 cases reached normal 7 weeks postpartum	136/96; 144/90
1 case reached normal 9 weeks postpartum	144/96
1 case reached normal 10 weeks postpartum	162/80
1 case reached normal 12 weeks postpartum	136/96
1 case reached normal 13* weeks postpartum	140/84
1 case reached normal 14 weeks postpartum	134/96
1 case reached normal 44 weeks postpartum	136/92

*After thyroidectomy for toxic adenoma.

Of the remaining 15 cases, 3 did not report for medical examination. The other 12 still had hypertension when examined. An analysis reveals:

CASE	MEDICAL EXAMINATION MADE	BLOOD PRESSURE
144-805	6½ weeks postpartum	130/100
141-848	8 weeks postpartum	172/120
40067	9 weeks postpartum	172/118
139-142	12 weeks postpartum	188/124
62333	14 weeks postpartum	142/98
90419	15 weeks postpartum	192/112
25230	22 weeks postpartum	178/110
140-263	31 weeks postpartum	138/88
141-335	34 weeks postpartum	192/124
89344	36 weeks postpartum	142/100
22154	39 weeks postpartum	172/98
68518	40 weeks postpartum	170/110

Laboratory Data.—1. The Wassermann Reaction: All 23 cases had a Wassermann done; only in 2 patients was it positive, and then only weakly so, being one-plus. Some years previously, however, it had been three-plus. Of the remaining

21 patients, 3 had received anti-syphilitic treatment during the recent pregnancy because of a previous positive reaction, or because of a history of having taken anti-syphilitic treatment at some other time. The latter is routine in our clinic to avoid any possible latent infection from escaping treatment during pregnancy.

2. Fischberg Concentration Test: This test was done on 16 of the patients. In 10 cases, it was low, the urine concentration never reaching the normal, 1.024. The remaining 6 cases revealed perfectly normal findings.

3. Phenolsulphonephthalein Excretion: Nineteen patients reported for this test. In 7 cases, it was 50 per cent or below for two hours. Three of this particular group also had a slightly subnormal Fischberg; 2 had normal Fischberg, and the remaining 2 patients had no concentration test done. On the other hand, in 6 cases of low urine concentration, the phenolsulphonephthalein excretion was normal.

4. Intake and Output: Of the tests done in 10 patients, 8 were normal. The other two, however, were far below par, the output being 18 per cent and 30 per cent of the intake (Cases 89344 and 62333). In both of these cases, the concentration test was normal, while the phenolsulphonephthalein excretion in the first case was 45 per cent, and normal in the latter case.

5. Blood Chemistry: This was performed on 18 patients, 15 of which were normal. The other 3 (Cases 102-504, 68518, and 25230) showed abnormally high uric acid content, being 6.12, 5.68, and 5.33, respectively.

6. Blood Picture: Blood counts were done on 18 patients; of this number, 6 had red cell counts of less than 4,000,000. Six also had a hemoglobin content of less than 70 per cent. None of the latter were in the former group.

Medical Examination.—Only 19 patients of the group presented themselves at the medical clinic for examination. Nine cases revealed sufficient evidence upon physical examination for a diagnosis to be made. These are:

Case 23632 Mild hyperthyroidism
Case 25230 Arteriosclerosis; possible chronic nephritis
Case 139-142 Congenital heart disease
Case 141-335 Arteriosclerotic heart disease
Case 77739 Hyperthyroidism
Case 82348 Syphilis; toxic adenoma
Case 22154 Heart disease; arteriosclerotic vs syphilitic; chronic nephritis
Case 62333 Toxic adenoma
Case 40067 Hypertensive heart disease

The following patients had no medical examination and the diagnoses given are merely made from the data available:

Case 136-967 Syphilis
Case 90076 Syphilis
Case 106-619 Syphilis; possible chronic nephritis
Case 47078 No diagnosis made

The remaining 10 cases had a physical examination but no evidence of any pathology, so that diagnosis was only possible from the laboratory data. These were:

Case 91300
Case 102-504
Case 43589
Case 68518
Case 142-464
Case 140-263
Case 89344
Case 144-805
} *Possible* chronic nephritis

No diagnosis could be made in Cases 141-848 and 90419.

Patients in This Series Who Are Pregnant at the Present Time.

CASE 90076.—Blood pressure was 156/104 at the six weeks postpartum examination. She did not return for medical examination and how long the hypertension persisted is not known. She is at the present time twenty-five weeks pregnant and her pressure has ranged from $\frac{98\text{-}118}{44\text{-}76}$.

CASE 68518.—Blood pressure ranged during last pregnancy from $\frac{110\text{-}126}{74\text{-}88}$. Six weeks postpartum it was 178/140. At the medical examination done when forty weeks postpartum it was 170/110. At present she is about thirty-two weeks pregnant and her pressure has been persistently high, ranging from $\frac{130\text{-}144}{80\text{-}90}$. This patient is in her seventh pregnancy and apparently is a chronic nephritic.

CASE 77739.—Blood pressure normal during pregnancy. At six weeks postpartum examination it was 162/80. Two weeks later, diastolic pressure rose to 110. Pressure returned to normal thirteen weeks postpartum. At the present time this patient is about twenty-seven weeks pregnant. Her pressure has ranged from $\frac{96\text{-}110}{50\text{-}70}$.

SUMMARY

1. Twenty-three cases, all colored patients, of postpartum hypertension following apparently normal pregnancy are described.

2. The incidence was found to be 4.6 per cent of all the postpartum cases examined, both white and colored.

3. Fifty-six per cent of the series were between twenty-one and thirty-one years of age.

4. 82.6 per cent of the patients were multiparas.

5. The average number of prenatal visits made was 9.

6. Sixteen patients in the series had blood pressure readings lower than 130/90 during pregnancy. The remaining 7 cases are added due to the marked rise postpartum. An analysis of this latter group is given.

7. All patients revealed increases in pressure at the routine six weeks postpartum examination.

8. Only in 8 patients in the series was it definitely established that a normal blood pressure was eventually reached.

9. The results of the laboratory work are shown.

10. Postpartum medical consultation showed definite organic disease in 9 cases.

11. Three patients in this study have become pregnant again, and an analysis up until the present time is given.

CONCLUSIONS

Hypertension, following normal pregnancy, is a relatively unstudied problem, since it has appeared in the literature only once previously.

Apparently it is predominately a disease of the colored race, although Stout has found the same condition in white women. The cause is unknown, but a few possibilities are suggested:

1. The result of the strain of labor. (This is improbable, since colored women usually have the easiest labors.)

2. The added stress put upon the kidneys in eliminating substances no longer necessary after pregnancy.

3. Since about one-third of the cases returned to normal seven to fourteen weeks postpartum, the cause might lie in an endocrine imbalance, in the attempt to become regulated to the normal, nonpregnant state.

I wish to express my appreciation for help and cooperation in examining these patients, to Dr. Charles Jones, of the medical clinic.

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THE BASAL METABOLIC RATE IN NORMAL PREGNANCY*

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THE basal metabolic rate during normal pregnancy is not thoroughly understood. While there are numerous articles in the literature concerning this subject, the various authors lack a unanimity of opinion as to the interpretation of their findings. It is generally conceded that the basal metabolic rate is increased during normal pregnancy, and is due to either of two factors, or a combination of them. These factors are: (1) The increased protoplasmic mass of pregnancy; and (2) simple hypertrophy and hyperplasia of the thyroid gland.

Moderate hypertrophy of the thyroid gland has been more or less generally accepted as incident to pregnancy, to meet physiologic needs. Slightly less than 50 per cent of pregnant women are said to have some enlargement of this gland. The majority of authors do not attempt to give any definite conclusions as to the cause for the varying increases in the basal metabolic rate that all of them report.

Root and Root state there is a marked increase in the basal metabolism during the latter months of pregnancy, both in the total number of twenty-four-hour calories and in the number of calories per unit of weight. Plass and Yoakam believe a rise in the basal metabolic rate greater than plus 15 per cent, with a slower return to normal, suggests increased thyroid activity incident to pregnancy. Murlin and others show an increase in the basal metabolic rate of plus 4 per cent. Many authors believe this rise so small as to be easily within the realm of normal error and variation. Williams writes that the increase in basal metabolic rate can be attributed

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to the growing products of conception and possibly a slightly increased activity of the thyroid gland. DeLee's only comment is that there is an increased basal metabolic rate during normal pregnancy, without hyperthyroidism. Hughes reports the largest number of basal metabolic readings, a total of 1250. His figures show a small increase at the sixth week of pregnancy, followed by lowered readings in the second, third, and fourth months; then, a gradual rise to a plus quantity, with a majority of the readings within normal limits, and in the last trimester an increase of plus 15 to 25 per cent. (This article seems to be the most complete in the literature from the clinical aspect.)

Supporting the theory of increased protoplasmic tissue as the cause for higher basal metabolic readings, Cornell and Baer report an abnormal rise in the basal metabolic rate during pregnancy, with a wide and nonconstant variation. They believe the death of the fetus in late pregnancy can be detected by a lowering in the maternal basal metabolic rate compared with the average of their series. This result they attribute to the cessation of the growth demands of the fetus and placenta. Sandiford and Wheeler found no evidence to suggest any change in the actual rate of intensity of heat production per unit mass of maternal tissue. Pommerenke, Haney, and Meek, by experimental work computing body surface areas of mother and baby rabbits and total heat production before and after delivery, conclude there is no actual increase in maternal basal metabolism.

Marine believes simple hypertrophy with some increased activity of the thyroid gland, amounting to more than enlargement incident to an increased blood supply, is present in women during puberty, menstruation, and pregnancy. Reycraft reports that up to 50 per cent of women in Ohio show enlargement of the thyroid during pregnancy, with a considerable increase in the basal metabolic rate. Seitz claims 70 to 80 per cent of patients show hypertrophic changes in the thyroid gland, due chiefly to increased vascularization and epithelial elements with a storage of colloid toward the end of pregnancy, and disappearing three or five days before the onset of labor. Bockelman and Scheringer report laboratory findings on the iodine content of the maternal blood: 15.5 gamma per cent at the second month, 22.5 gamma per cent at the tenth month, and a definite decrease during the first two weeks postpartum. Stewart and Menne concluded from experimental work on pregnant rabbits that there is limited but definite evidence that iodine lowers basal metabolic shock incident to pregnancy. This conclusion is based on lowered basal readings and less active thyroid glands recorded for animals receiving iodine daily.

Actual increases in basal metabolic readings during pregnancy recorded in the literature range from plus 4 per cent to plus 35 per cent above normal just prior to the onset of labor. Practically all authors agree that there is a gradual return to the normal level during the first ten to fourteen days postpartum.

Many difficulties are encountered in the making of basal metabolic rates, and, despite all carefulness and precaution, various extrinsic factors may affect this examination of the patient.

The technic used in obtaining the basal metabolic rates in this series of cases is as follows:

1. Patient was at rest in bed for twelve to fourteen hours previous to the beginning of the test.

2. Patient given nothing by mouth except water, and not that for two hours previous to the beginning of the test.

3. Majority of the tests made by the same two individuals.

4. Sanborn portable motorgraphic machine used. The examination is based on the amount of oxygen consumed by the patient in a period of any consecutive eight minutes.

5. Examinations were made approximately at the fifth and the ninth lunar months and on the ninth day postpartum.

6. Patients examined, only those women having an apparently normal and healthy prenatal course.

The following results were obtained (figures indicate rate above zero):

I. Total Cases

(No omissions for any cause)

	PREGNANCY		POSTPARTUM
	1.	2.	3.
Number of basal metabolic rates in group	57	30	52
Average number of days of pregnancy or puerperium	133	245	9
Average weight of patients (pounds)	124.44	141.53	123.64
Average basal metabolic rate	8.2	14.6	4.1

(Omitting 5 cases from group as only first basal metabolic rate was done)

	1.	2.	3.
Number of basal metabolic rates in group	52	30	52
Average number of days of pregnancy or puerperium	143	245	9
Average weight of patients (pounds)	124.44	141.53	123.64
Average basal metabolic rate	8.3	14.6	4.1

(Omitting 9 cases because the rates do not follow the general trend of the readings)

	1.	2.	3.
Number of basal metabolic rates in group	34	21	34
Average number of days of pregnancy or puerperium	144	245	9
Average weight of patients (pounds)	127.24	144.07	126.27
Average basal metabolic rate	9.7	15.6	2.4

II. Cases With All Three Basal Metabolic Rates Done on Patient

(No omissions)

	PREGNANCY		POSTPARTUM
	1.	2.	3.
Number of patients in group	30	30	30
Average number of days of pregnancy or puerperium	133	245	9
Average weight of patients (pounds)	123.98	141.53	124.18
Average basal metabolic rate	8.5	14.1	4.9

(Omitting 9 cases because they do not follow the general trend of the readings)

	1.	2.	3.
Number of patients in group	21	21	21
Average number of days of pregnancy or puerperium	133	245	9
Average weight of patients (pounds)	126.54	144.07	126.1
Average basal metabolic rate	6.7	15.6	3.5

III. Cases With Only Two Basal Metabolic Rates Done

(No omissions)

	PREGNANCY		POSTPARTUM
	1.	2.	3.
Number of patients in group	22	0	22
Average number of days of pregnancy or puerperium	155	0	9
Average weight of patients (pounds)	125.47	0	122.9
Average basal metabolic rate	8.1	0	3.1

(Omitting 9 cases because they do not follow the general trend of the readings)

	1.	2.	3.
Number of patients in group	13	0	13
Average number of days of pregnancy or puerperium	147	0	9
Average weight of patients (pounds)	129.44	0	126.56
Average basal metabolic rate	14.1	0	0.6

IV. Cases With Only One Basal Metabolic Rate Done on Patient

	PREGNANCY		POSTPARTUM
	1.	2.	3.
Number of patients in group	5	0	0
Average number of days of pregnancy or puerperium	127	0	0
Average weight of patients (pounds)	122.65	0	0
Average basal metabolic rate	11	0	0

There were no patients included in these groups who showed any signs clinically of any thyroid disturbance, although approximately 40 per cent showed slight enlargement of the gland to palpation. Eleven patients showed various signs of mild toxemia of pregnancy. The average basal metabolic rate for them:

Group I	18	19	16	(5 cases)
Group II	11		3	(6 cases)

There were no cases of severe toxemia. One case of eclampsia developed in a patient who did not attend clinic regularly. She was delivered in another hospital by cesarean section, and no postpartum basal metabolic rate was done.

Spontaneous Cases

		Group I			Group II		
Morbid	(4 cases)	15	13.6	8.7	(5 cases)	7.4	11.0
Nonmorbid	(16 cases)	7	13.0	2.2	(16 cases)	9.9	0.6

Operative Cases

		Group I			Group II		
Morbid	(2 cases)	3.5	11.0	0.5	No cases		
Nonmorbid	(8 cases)	9.4	19.2	10.6	(1 case)	-16	3

There were 30 patients who had the complete study of three basal metabolic rate tests; two prepartum, at approximately the fifth and the ninth lunar months, and one postpartum on the day before discharge from the hospital, usually the ninth day.

SUMMARY

The basal metabolic rate during normal pregnancy is increased above the normal for that particular patient and this reading (29 to 33 cases) is usually but not always, within the generally accepted limits of plus and minus 10. Occasionally an excitable patient had a basal metabolic rate higher than the average for this series. At the ninth lunar month the basal metabolic rate occasionally increased 33 points above the reading at the fifth lunar; generally it was only slightly elevated above the usual normal limits, but sometimes was a higher reading than expected. Occasionally the reading was lower at the second reading, thought due to an abnormal first reading at the fifth month. By the ninth day postpartum practically all basal metabolic rates (41 in 11 cases) were within normal limits and usually but not always somewhat below the level of the reading at the fifth lunar month. While no method was used to determine the cause of this slight increase in the basal metabolic rate, it is our impression that the cause is a combination of increased protoplasmic mass activating a slightly increased activity of the thyroid gland.

CONCLUSIONS

1. At the fifth lunar month of pregnancy, the basal metabolic rate is within normal limits (plus and minus 10).

2. At the ninth lunar month of pregnancy, the basal metabolic rate is slightly elevated (plus 14 to plus 16).

3. On the ninth day postpartum, the basal metabolic rate is again within normal limits, but usually slightly below the basal metabolic rate at the fifth lunar month.

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DISCUSSION

DR. CHARLES MAZER.—The conception of the mechanism of thyroid hyperplasia during pregnancy requires elucidation. It is not a physiologic manifestation to meet the need for thyroxin by the growing embryo, but rather a pathologic

manifestation of an actual or a relative deficiency of iodine in the pregnant woman. The administration of small doses of iodine or the iodine-containing hormone, thyroxin, in the pregnant woman who develops even a slight enlargement of the thyroid or the one whose basal metabolism is far short of plus 15 per cent during the second half of pregnancy is, in my opinion, rational therapy.

The relatively low basal metabolic rate found at or near term in this series of cases is unique. Most investigators have found a much higher basal exchange during advanced pregnancy of normal women.

DR. PENDLETON TOMPKINS.—In looking over the statistics on the percentage of patients with enlargement of the thyroid during pregnancy, one finds a discrepancy of 40 per cent in Philadelphia and 80 per cent quoted by Murray and 60 per cent by Bloss. That difference can be explained by the difference in the probable iodine intake in those areas. As one passes farther and farther into the goiter belt, the incidence is higher.

Two groups of pregnant patients have been studied in parallel series, one receiving iodine as a matter of routine and one receiving none. I believe that in the group receiving iodine there were no hypertrophies and in the other there was the same percentage of hypertrophy as in the population in general. This supports Dr. Mazer's point.

A SUPERIMPOSED LIPEMIA DURING LABOR*

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IN SOME studies on the lipemia of pregnancy[10, 15] analyses were made on blood taken at the end of parturition. There are a number of possible factors apart from pregnancy itself which conceivably might affect results obtained at that time. The anesthesia during delivery, the loss of blood, psychic disturbances, and labor itself are some of these. When values for blood lipids determined at the conclusion of labor are compared with values taken before labor[1] no marked differences are noted. For this reason no one has apparently considered the possibility that labor itself may affect blood lipid concentrations. In the present investigation, it was found that labor itself, when studied separately from the effect of the anesthesia and loss of blood during delivery, superimposes upon the lipemia of pregnancy a further lipemia. An indication that such was the case was revealed when by chance two samples of blood were taken from a parturient woman at different stages during labor.

Proceeding from this observation, 16 patients were studied from the Obstetrical Service of the Kingston General Hospital. A sample of blood was taken as soon as possible after the patient has gone into labor and a second sample just before administering anesthesia prior to delivery. There was necessarily considerable variation in the interval

*This work was aided financially by the Alice F. Richardson Fund of the Kingston General Hospital.

between samples. The shortest time was one and one-half hours and the longest was twenty-four hours. The average interval was ten hours and the median was eight hours. With an interval of less than two hours, the difference in lipid values of the two samples was slight. Between six and twenty-four hours, the differences in lipid values increased but very little with increase in the time. Hence, the superimposed lipemia of labor must occur largely in the last few hours of labor. When it was impossible to obtain the second sample of blood before giving anesthesia, the case was not included in the series. Anesthesia itself influences the concentration of blood lipids, affecting chiefly the red blood cells.

The anticoagulant used was heparin, in a concentration of 10 mg. per cent, because heparin has much less effect upon the partition of blood lipids than the anticoagulant salts. The first sample of blood was stored in the ice box until the second sample was ready and then both were centrifuged at full speed for one hour. It was found that no change occurred in the lipid values of heparinized blood stored for as long as three days in the ice box. Hence the differences observed in the lipid content between Samples 1 and 2 could not have been due to Sample 1 having stood longer than Sample 2. Plasma and red cells were extracted with 25 volumes of alcohol-ether, no heat being used,[4] and the extracts were analyzed by the oxidative micromethods of Bloor as employed in previous investigations.[1-4]

It was found impossible to insist upon fasting the patients previous to the withdrawal of blood. The diet of these women before their admission to hospital was unknown. In most instances the patients had been in labor some hours before admission and under such circumstances probably took little food. Certainly those in active labor had little taste for food until some hours after delivery. As emphasized in a previous communication,[3] ordinary meals have practically no effect on the lipid content of blood of normal individuals but their effect on blood lipids of pregnant women is unknown.

Seven of the 16 women were primiparous and 11 were multiparous. Their ages varied between seventeen and thirty-eight years. No toxic signs or symptoms were evidenced by any of the cases.

RESULTS

The values determined by this differential lipid analysis included: total lipid, neutral fat, total fatty acids, phospholipid fatty acids, cholesterol ester fatty acids, neutral fat fatty acids, total cholesterol, ester cholesterol, free cholesterol and phospholipid. A total of 640 such values formed the basis of the present report. A statistical summary of these results is presented in Table I. The formula used for calculating the standard deviation of the mean has been previously given in this JOURNAL.[2]

The significant changes observed occurred only in plasma. In this part of blood, an increase was demonstrated in the majority of cases in all lipid values except those of ester cholesterol. The total lipid content of plasma increased during labor in 87 per cent of cases from an average initial value of 787 mg. per cent to a mean of 844 mg. per cent just before delivery. The mean increase of 57 mg. per cent had a standard deviation of 43 mg., indicating that in over 5 out of 6 cases one may expect an increase in total lipid during labor. The result was therefore statistically significant. The increases were slight. The mean increase in total lipid was but 7.3 per cent and the greatest increase was 14.2 per cent. During labor, thus, there occurs a superimposed lipemia which is not extensive but is consistent.

TABLE I. VARIATIONS IN THE LIPID CONTENT OF BLOOD DURING PARTURITION IN SIXTEEN PATIENTS.

VALUE	AVERAGE INITIAL VALUE (MG. %)	AVERAGE VALUE AT DELIVERY (MG. %)	AVERAGE CHANGE (MG. %)	STANDARD DEVIATION OF CHANGE (MG.)	NO. OF CASES SHOWING INCREASE (%)	AVERAGE PERCENTAGE CHANGE (%)
Blood Plasma						
Total lipid	787	844	+57	43	87	+7.3
Neutral fat	236	264	+28	27	62	+11.9
Total fatty acid	480	523	+43	30	94	+9.0
Total cholesterol	212	215	+3	25	62	+1.4
Ester cholesterol	140	135	−5	21	44	−3.6
Free cholesterol	72	80	+8	7	94	+11.1
Phospholipid	245	271	+26	17	100	+10.6
Red Blood Cells						
Total lipid	451	435	−16	21	44	−3.6
Neutral fat	61	52	−9	22	38	−14.7
Total fatty acid	247	237	−10	31	38	−4.1
Total cholesterol	112	112	0	11	50	0.0
Ester cholesterol	16	13	−3	9	19	−18.7
Free cholesterol	96	99	+3	6	69	+3.1
Phospholipid	268	268	0	22	44	0.0

The increase in total lipid was due to increases in neutral fat, free cholesterol, and phospholipid. In most lipemias such as those of normal pregnancy, diabetes mellitus, nephritis, and hypothyroidism, the lipid increased most in value is plasma neutral fat. On the average, neutral fat also increased more than any other lipid in the superimposed lipemia of labor. The relative increase in plasma neutral fat was not very much more than that of free cholesterol or phospholipid. There were more exceptions showing a slight decline in neutral fat values than in the case of the other two lipids. The fact that such decreases in plasma neutral fat were slight is seen from the mean changes and their standard deviation as shown in Table I. From this one may conclude that 5 out of 6 cases may be expected to show an increase in plasma neutral fat content during labor.

Values for plasma phospholipid showed the most consistent increase, this occurring in all of the cases. The greatest increase in phospholipid was 29 per cent and the least 1.8 per cent, the average increase being 10.6 per cent. Plasma free cholesterol values were raised relatively about the same extent as phospholipid and 15 of the 16 cases showed an increase.

Ester cholesterol of plasma fell in concentration during labor. A decrease in the ester cholesterol content while other plasma lipids are increasing has been previously noted in the lipemia of pregnancy in guinea pigs[7] and in women[9] and in nephritic lipemia.[5] Boyd[6] has described the interrelation of plasma lipid values with increasing total lipid and noted this eccentric change in ester cholesterol. Lipopenic variations in ester cholesterol have been missed apparently in less complete studies of other lipemias. Its significance is obscure. As a result, there was relatively little change in total cholesterol and the mean increase in total fatty acids was relatively less than that of phospholipid or of neutral fat.

On the average there occurred a decrease in the lipid content of the red blood cells during labor (Table I). In all instances, however, the standard deviation of the mean change was greater, and considerably greater, than the average change itself. This emphasizes that the changes were not consistent and this may also be seen in the column listing the number of cases showing an increase. In 81 per cent of cases there was a decrease in the ester cholesterol content of the red blood cells but all of these values were so low and the average loss so little that it is doubtful if the decrease be significant. One may conclude that the superimposed lipemia of labor is a phenomenon affecting plasma and not the red blood cells.

Of the various possible causes, muscular exercise would appear to be the most likely factor responsible for the superimposed lipemia of labor. Patterson[13] showed that exercise produced a lipemia; Stewart, Gaddie and Dunlop[16] confirmed this and noted that interrupted work periods produced a more marked lipemia. Fahrig and Wacker[8] found that exercise increased cholesterol, cholesterol esters and "lecithin" as well as fat although others[16] had noted an increase only in neutral fat. Houget[11] also noted a general increase in all lipids of blood following exercise in dogs. More strenuous exercise in the experiments of Stewart, Gaddie, and Dunlop[16] would probably have resulted in a general rise in all blood lipid values rather than only in neutral fat as they found. By analogy, it would appear probable that the muscular exercise of labor is the factor responsible for the superimposed lipemia of labor.

Severe muscular exercise has frequently been found to produce an increase in blood hemoglobin and the red cell count. Schneider and

Crampton[14] attribute this to anoxemia plus other undetermined causes. Others[12] have suggested it is due to the effect of increased amounts of lactic acid in blood causing contraction of the spleen. There was no consistent change in the hemoglobin and red cell count in the present series of cases. In half of the cases they were increased and in half decreased during labor. In about two-thirds of the cases the percentage volume of the red cells rose during labor. There were insufficient cases to permit of a definite decision but the results suggested that possibly the volume of the red cells may increase during labor. This was not accompanied by any significant change in their lipid content.

SUMMARY

Heparinized blood was analyzed by oxidative micromethods and taken from 16 patients on two occasions, early and late in labor. It was found that during labor there occurred a significant increase in plasma phospholipid, free cholesterol and neutral fat with no change or a decrease in plasma ester cholesterol. There were no significant changes in the lipid content of the red blood cells. The results demonstrate the occurrence of a superimposed lipemia during labor which is probably due to muscular exercise.

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Vignes, H.: Pruritus Among Pregnant Women, Gynécologie **36**: 88, 1937.

Vignes has observed 41 women who had vulvar and perivulvar pruritus during pregnancy and 15 women who had nonvulvar itching. These occurred in a series of 1,800 pregnant women. In 27 of the 41 cases there were no lesions but in the remaining 14 cases there were skin manifestations such as eczema, intertrigo, vulvitis, etc. Most of these patients reported that the pruritus began in the sixth month of pregnancy. In many cases, varicose veins were present and these were of etiologic significance. Six women had leucorrheal discharges. Vignes found that 19 women had definite evidence of syphilis, a few had hyperthyroidism, a few glycosuria, five had excessive vomiting or ptyalism, three had psychic disturbances and three had pruritus after arsenic therapy. Treatment gave quick relief in most cases.

J. P. Greenhill.

MYXEDEMA WITH MENORRHAGIA AND TETANY AS COMPLICATIONS FOLLOWING A PARTIAL THYROIDECTOMY*

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THE purpose of this communication is to report a case of secondary postoperative parathyroid insufficiency, occurring in a negress, single, aged thirty-six years, who had a bilateral partial thyroidectomy three months prior to the onset of the menorrhagia and postoperative myxedema and the complication of tetanic convulsion and spasms.

Eason[1] in 1915 reported a case of myxedema with tetany, and Barker[2] cites that Frankl-Hochwart pointed out that struma was present in 13 of 26 cases of idiopathic tetany and mild myxedematous symptoms appeared in chronic tetany. In such cases, favorable results were obtained with thyroid extract on the trophic changes associated with tetany.

Pidoux,[3] basing his opinion on his observations of six cases of parathyroid tetany in spontaneous myxedema (Pidoux, Eason, Lifschitz, Cantonnet, Morwitz, Kropehn) concludes that symptoms of parathyroid insufficiency may develop in myxedema or remain latent. The myxedema can be of congenital or acquired origin and has also been noted in Brissaud's infantilism.

Forsyth, quoted by Pidoux, observed changes in the parathyroid glands in a fatal case of myxedema. Engelbach,[4] quoting various authors, states chronic tetany is likely to become acute in weak, anemic individuals, and tetany occurs during pregnancy as the result of severe hemorrhages and the loss of blood calcium, or when the increased calcium demands of the fetus are not met, due to the previously impaired parathyroid glands of the mother.

Kepler[5] has observed tetany associated with myxedema but is of the opinion it is an infrequent complication of myxedema, and the literature on the subject supports this opinion.

CASE REPORT

J. S. was admitted on May 27, 1936, to the service of Dr. William R. Nicholson at the Graduate Hospital with the diagnosis of menorrhagia. *Previous illness:* syphilis (antisyphilitic therapy), appendectomy.

History of Present Illness.—Patient had bilateral partial thyroidectomy three months ago (Feb. 27, 1937) and was discharged in good condition with a basal metabolism rate of minus 15. On May 6, 1936, the regular menstrual period occurred; the flow was excessive (12 pads a day). Large clots were expelled and the period lasted for two weeks. Vaginal bleeding stopped for four days and reappeared three days ago. For twenty-four hours preceding admission to the hospital she had vaginal hemorrhage and extreme weakness.

Physical Examination (made by Resident Physician on admission).—The patient is extremely listless, in great contrast to the hyperthyroid patient of three months ago. She has gained over 30 pounds in three months, and is obese. *Skin and mucous membrane:* pale. *Pulse:* 75; *Respiration:* 20. *Temperature:* 96° F. *Blood pressure:* 130/80. *Scalp: Hair:* short and coarse. High forehead line. *Eyebrows:* outer half very thin. *Face:* myxedematous appearance. *Skin and Scalp:* dry; generalized myxedema. *Speech:* thick; deep-toned. *Mental reactions:* sluggish. *Eyes:* moderate exophthalmus; pupils react to light and accommodation. *Ears and Nose:* negative. *Teeth:* dental caries. *Throat:* negative. *Cardiac:* only poor quality second sound

*Read before the Obstetrical Society of Philadelphia, May 6, 1937.

heard over the heart. No murmurs. *Abdomen:* no masses palpable. *Liver and Spleen:* not palpable. *Extremities:* nonpitting edema. Thick subcutaneous tissue. *Vaginal Examination:* excessive bleeding; *vagina* filled with clots. *Uterus:* no evidence of abortion.

LABORATORY DATA

May 9, 1936: *Urine* (chemical and microscopic) negative. Specific gravity, 1005 to 1013. *Blood:* R. B. C., 1,000,000. Hb, 58 per cent. W. B. C., 6,800. Neutrophile, 68 per cent. *Blood chemistry* (per 100 c.c. of blood): Chlorides, 479 mg. Cholesterol, 190 mg.

June 3, 1936 (after calcium therapy): Calcium, 9.6 mg. Phosphorus, 4.8 mg.

CLINICAL DATA

Temperature Range.—From 96° F. on admission to 104°. Elevated temperature subsided two days before onset of tetanic convulsions. Blood pressure: systolic 100 to 130; diastolic 60 to 92.

CONTINUATION NOTES

Immediate Therapy.—The usual operative gynecologic procedures in hemorrhage and its shock were instituted; however, bleeding promptly recurred, and on May 29, 2 c.c. of A.P.L. (Collip) were administered intramuscularly every eight hours; thyroid extract, 3 gr. t.i.d. for forty-eight hours, and then 1 gr. t.i.d. was ordered. Fluid intake of 5,500 c.c. with a urinary output of 2,600 c.c. Blood pressure (mm. of mercury): systolic 100; diastolic 60. *May 31:* excessive uterine bleeding controlled.

June 1, 1936: Tetanic convulsion, preceded by severe tetanic cramps and extremely painful flexions of thighs, knees, ankles, and toes.

Therapy.—Calcium gluconate (1 gram) intravenously. Morphine sulphate gr. ¼ and scopolamine gr. $\frac{1}{150}$. Calcium gluconate 1 gm. orally every 4 hours. Viosterol M XV daily.

June 3, 1937: Nausea and spasm of toes. Intravenous calcium gluconate, 1 gm., given.

Condition on Discharge.—No evidence of myxedematous swellings, and no vaginal bleeding for past eight days. Mentally bright. No signs or symptoms of tetany.

Therapy.—Thyroid, 2 gr. daily. Calcium chloride X gr. t.i.d. Viosterol XV M daily.

Bilateral partial thyroidectomy is the most frequent cause of parathyroid insufficiency and tetany; however, parathyroid tetany usually, but not always, occurs shortly after the thyroid operation. The onset of the tetany syndrome is rapid if the parathyroid glands are unintentionally removed, and latent if due to injury to the parathyroid tissues or their blood supply. The severity and duration of the symptoms depend upon the degree of the subnormal level of the blood calcium; convulsions usually occur when the calcium falls below 7.5 mg. per 100 c.c. of blood; the neuromuscular hyperirritability, spasms, Erb and Chovstek signs appear at the lesser subnormal blood calcium levels. Blood phosphorus rises as the blood calcium falls.

The parathyroids, the thyroid, and very likely, the anterior pituitary gland, are directly concerned in calcium metabolism and blood calcium.

Hyperthyroidism depletes the body calcium reserves and generalized osteoporosis frequently results; accordingly we feel that, exclusive of the factor of thyroid surgery, there are other factors responsible for the low blood calcium level and the tetanic syndrome: (1) lowered or depleted calcium stores due to the recent hyperthyroidism, (2) myxedema and the lack of thyroid mobilizing effect on calcium, and (3) lowered blood calcium level due to severe and prolonged hemorrhage.

It is our belief that in the case presented, the hemorrhage was the precipitating cause of the low blood calcium and the tetanic syndrome. The pulse of myxedema is bradycardic, therefore the pulse rate of 72 to 82 presents, at least, a 50 per cent increase in the abnormally low pulse rate, and is of a hemorrhage range and type.

The prompt disappearance of the tetany syndrome after the administration of calcium, as well as the posttherapeutic level of 9.6 mg. of calcium per 100 c.c. of blood, indicates the low pretherapeutic blood calcium level as the cause of the tetany.

With a history of bilateral partial thyroidectomy, and the above three factors directly affecting blood calcium metabolism and content, consideration of other clinical conditions causing tetanic spasms or convulsions appear unnecessary, since no diagnostic signs or symptoms exist which suggest their possible inclusion.

More important than the anatomic-pathologic diagnosis or clinical diagnosis is the therapy of menorrhagia as a symptom of myxedema. In 15 of the 59 cases studied by Gardner-Hill[6] a major pelvic operation or x-ray therapy was resorted to for induction of artificial menopause to control the menorrhagia. These are major measures as compared to thyroid therapy, in menorrhagias of hypothyroid origin.

Early diagnosis of the hypothyroid menorrhagia is required because thyroid therapy has a distinct disadvantage as an emergency therapeutic agent. While intravenous thyroxin injection produces therapeutic effects earlier than oral therapy, still, ten days must pass before its full therapeutic effect is obtained. Thyroid extract requires even a longer period to act, consequently all forms of thyroid therapy in this and corresponding cases are of little value in the emergency control of the hemorrhage from a myxedematous uterus.

In this case, supplementing the gynecologic therapy, A.P.L. (Collip) was administered; 2 c.c. intramuscularly every eight hours for 4 doses. The bleeding was controlled in thirty-six hours. (We are indebted to Ayerst, McKenna and Harrison, Rouse's Point, N. Y., and Montreal, Canada, for the supply of Collip's A.P.L.)

Twelve hours later, a tetanic convulsion, preceded for a short time by cramps of the lower extremities, occurred, and 1/4 gr. of morphine sulphate, and 1/150 gr. of scopolamine. Orally 4 gm. of calcium gluconate was administered and 15 minims of viosterol daily. The tetanic convulsion was controlled by this therapy. A second intravenous calcium gluconate injection was given two days later when nausea and spasm of the toes appeared. The first blood calcium determination was reported on June 3, 1936, after calcium therapy had been started, and was 9.6 mg. calcium and 4.8 mg. phosphorus, and on this day the spasm of the toes reappeared, and intravenous calcium, 1 gm., was given.

The onset of the symptoms did not permit estimation of the blood calcium prior to the administration of calcium.

Under similar circumstances, should intravenous thyroxin be administered in preference to oral thyroid therapy? In this manner, earlier complete arrest of hemorrhage might be possible, however, over-effect of thyroxin is possible. Since the dosage of thyroxin must be estimated by basal metabolism rate determinations, the dosage of thyroxin in these circumstances must be empirical and lean to under-effect in preference to the possibility of causing hyperirritability from thyroxin nerve effect in a patient already having a supersensitive neuromuscular mechanism due to calcium deficiency. Under such conditions, oral therapy, which can be better controlled, seems advisable.

CONCLUSIONS

The menorrhagia, which was the first abnormal menstrual period, occurred three months after the bilateral partial thyroidectomy and coincident with the myxedematous state. The menorrhagia lasted fourteen days, ceased for four days, recurred and lasted five days more. The tetanic manifestations appeared twenty-four days after the onset of the menorrhagia, and three and one-half months after partial bilateral thyroidectomy.

The postoperative period presenting negative evidence of parathyroid insufficiency, the case is best classified as a secondary postoperative parathyroid insufficiency because pathologic uterine bleeding due to the postoperative myxedema lowered the blood calcium, and since the parathyroids were incapable of elevating the blood calcium to normal, the tetanic syndrome occurred and the latent state of parathyroid insufficiency became apparent.

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DISCUSSION

DR. WILLIAM BATES.—The combination of factors in this case has proved quite interesting. Tetany due to injury or removal of parathyroid glands at the time of thyroid operations, occurs within six to eight hours after operation. In this case there was no such time relationship between partial thyroidectomy and the tetany seizures.

The only basal metabolic rate taken on the admission for hemorrhage showed a plus 18 to 23. This basal metabolism rate was taken on May 29, two days after admission, and after the administration of only 3 gr. of thyroid extract. There is no doubt in my mind that there are other factors than the thyroid function concerned with the rate. However, we apparently have here clinical evidence of deprivation of thyroid tissue and the tetany might be called thyroprival tetany which is a recognized classification.

There are several types of tetany encountered, such as rheumatic tetany, gastric tetany, hyperventilation tetany, latent tetany, parathyroid tetany, parathyroprival tetany, and thyroprival tetany.

However, until the calcium in circulation was depleted by hemorrhage, tetany did not occur in this case. Therefore, she is probably a potential parathyroprival or a potential thyroprival. By potential, I mean a type requiring some assisting factor, such as hemorrhage or other factors that lower blood calcium, to produce actual tetany. Therefore we are using the terms, secondary and potential, interchangeably, as meaning the need of assisting calcium depletion.

DR. DUNN (closing).—Yesterday a single girl of twenty-six years of age consulted me and gave the following history. In June, 1936, she had had a dilatation and curettage for severe hemorrhage. That was followed in ten days by laparotomy; part of the left ovary and half of the right ovary were removed. The hemorrhage recurred for thirteen weeks, and she was readmitted and dilatation and curettage were again performed which also did not stop the recurrent uterine hemorrhage, and dilatation and curettage and radium were given.

This girl had given a history of a basal metabolism of minus 20 for seven years. It was known in 1934 that she had a basal metabolism of minus 20. Thyroid was given, but because of a toxic reaction it was discontinued. Subsequently she had the above operations and the menorrhagia persisted.

I feel, as Gardner pointed out in his paper, the subject of hypothyroid menorrhagia is neglected. There is very little in the literature about thyroid therapy in the control of menorrhagias. Nothing will adequately control this girl's bleeding until she receives sufficient thyroid therapy.

A LATERAL VAGINAL WALL RETRACTOR*

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RELAXED vaginal walls may be a detriment in applying the cautery to the uterine cervix because the lateral vaginal walls tend to fold between the blades of the ordinary speculum. These lateral walls not only obstruct the view of the cervix, but are likely to be touched by the shank of the cautery wire.

Fig. 1.—Lateral vaginal wall retractor.

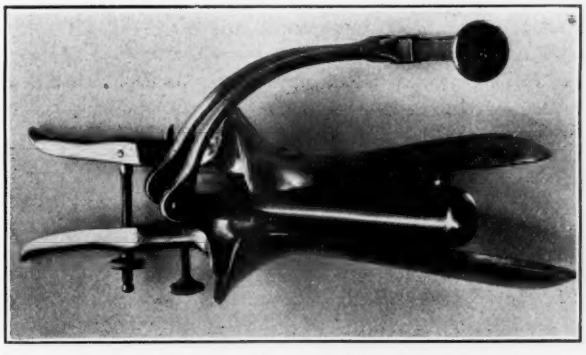

Fig. 2.—Blades of lateral vaginal wall retractor in place between blades of the speculum.

The lateral vaginal wall retractor assists in keeping the vagina adequately opened. It is placed in position after the speculum has been opened. The handles are hinged, so that they can be either elevated or depressed.

*Submitted for publication, January 2, 1937.

This instrument is manufactured by V. Mueller and Co., Chicago, Ill.

Department of Book Reviews

Conducted by Robert T. Frank, M.D., New York

Review of New Books

Obstetrics

In response to an invitation from the publishers Weibel has undertaken the writing of two volumes, *Lehrbuch der Frauenheilkunde,*[1] the "healing art of women," a literal translation but a poor expression, on the combined study and practice of obstetrics and gynecology. He realizes the close intimacy of the two subjects, but does not avoid stating there are wide differences as well.

In this first volume, which deals mostly with obstetrics, he develops the sections on anatomy and physiology to cover all phases, bringing out the recent contributions on hormones. The discussion of normal pregnancy, diagnosis, physiology and hygiene is marked by its clarity and conciseness.

The mechanism of labor and its conduct are well presented. The sagittal section illustrations give an excellent portrayal of the processes involved in the various steps of delivery, and the serial roentgenographs of a spontaneous delivery, afford an excellent means of observing the attitudes of the fetus at different stages. The mechanism of the third stage is illustrated in a similar way, the placental vessels having been injected with an opaque substance. All the abnormal presentations are illustrated in a double manner, cut out section drawings and roentgenographs. This method of pictorial demonstration leaves almost nothing to be desired in the way of explanation.

In discussing anesthesia in labor, Weibel refers pointedly to the frequent disadvantages resulting, such as prolonged labor and enforced interference, as well as to the occasional danger of intrauterine death of the fetus when some of the recently proposed methods of amnesia are employed.

In discussing toxemias, hyperemesis gravidarum, the nephropathies as a group, and eclampsia are section titles. Weibel places all nonconvulsive toxemias under the second heading. He regards them as nephroses, though stating that an eclamptic convulsion may ensue if the condition progresses. Further stages he terms "eclampsism," then preeclampsia, and finally eclampsia. For the latter he recommends the conservative treatment of Stroganoff, although substituting sodium luminal for chloral hydrate.

There is a very fine discussion of the treatment of placenta previa; the different methods of delivery are fully dealt with in regard to the type of previa. Weibel appears to favor cesarean section, though he seldom expresses a very marked personal note in the text. While the pathologic aspect of puerperal sepsis is thoroughly presented, the outline of treatment is confusing. Weibel lists eleven drugs of proprietary type as of therapeutic value, but does not mention sulfanilamide.

The discussion of operative procedure is succinct and brief. The forceps of both Naegele and Kielland are discussed, the latter model is shown in all the illustrations of delivery by forceps.

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[1]**Lehrbuch der Frauenheilkunde** (in zwei Baenden). Von Professor Dr. W. Weibel, Vorstand der II. Universitaets-Frauenklinik in Wien. Erster Band: Geburtshilfe. Mit 849 zum Teil mehrfarbigen Abbildungen im Text und 16 farbigen Tafeln, 647 Seiten. Urban und Schwarzenberg, Wien, 1937.

The book is profusely illustrated and the imprint is good, but the binding in paper is really worthless. The book serves as an example of present-day teaching and practice from the Vienna school, but lacks any personal note.

—*Philip F. Williams.*

On the foundation stones of his third edition of the textbook on *Operative Midwifery,* published in 1916, Dr. Kerr has erected a truly monumental textbook of *Operative Obstetrics.*[2] There are 832 pages of text and 338 illustrations. In the preparation of this fourth edition, the author has had the assistance of Dr. Donald McIntyre and Dr. D. F. Anderson. The American literature of recent years is widely quoted to so recent a time as within six months before publication.

The keynote of the present edition as in the previous one lies in the discussion of the knowing "when and how" to interfere. Particularly does Dr. Kerr stress the need for experience in obstetric surgery where the finesse and timing of intervention play so important a rôle.

Primarily, he discusses dystocia from the general aspects of the forces, the child and the passage, and the recognition of the early indications for interference. From this he passes to answering the question "how far can dystocia be prevented?" In elucidating the answer he presents chapters on obstetric diagnosis, radiography, examinations in labor, conduct of labor and the series of discussions on the prevention of infection, prevention of trauma and the subject of injury to the fetus.

After an analysis of the anomalies and faults in the forces, he passes on to the very detailed consideration of those instances, where, in labor, the cause of the dystocia can be found in the fetus. The treatment of occipitoposterior reflects the long experience of the author in abnormal obstetrics. He enumerates those symptoms and signs which are indicative of probable rotation and spontaneous delivery and those indicative of probable persistence of the posterior position. He attaches great importance to the manual correction of the shoulders as an aid in rotation. He feels that early conversion of the mentoposterior positions should be followed by successful delivery; for mentoposterior positions in the hands of the general practitioner he recommends version.

Kerr feels that all primigravidas with breech presentation should be confined in the hospital under the care of an expert operator. He regards external cephalic-version as the accepted treatment for breech presentations at the thirty-sixth week. The proposition of Burns and Marshall for the after-coming head should receive extended trial. Quoting figures on fetal mortality in breech presentations, the author states that the fetal death rate in this presentation should not be higher than four to six per cent in primiparas. There is an excellent discussion of oblique and transverse lies as well as of those due to congenital and anomalous conditions of the fetus, monsters, which in themselves cause dystocia. He recommends the wider use of radiography. The various complications of multiple births are discussed with the advice that the less interference the better.

The subject of dystocia due to contracted pelvis, and the many clinical and radiological methods of diagnosis are presented quite fully. There are many quotations from American authorities on this subject. Dystocia resulting from abnormalities affecting the soft parts, parturient canal, and its adjoined or adjacent structures is handled in the most comprehensive manner. The teaching for such conditions corresponds closely to the consensus of opinion in the United States.

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[2]**Operative Obstetrics,** A Guide to the Difficulties and Complications of Obstetric Practice. By J. M. Munro Kerr, LL.D., M.D., F.C.O.G., Emeritus Regius Professor of Midwifery, University of Glasgow, Obstetric Surgeon, Glasgow Maternity Hospital. With the assistance of Donald McIntyre, M.D., F.C.O.G., Consulting Obstetric Surgeon, Barshaw Maternity Hospital and D. Fyfe Anderson, M.D., Senior Assistant to Professor of Obstetrics and Gynecology (Muirhead Chair) Glasgow University, With 338 Illustrations, William Wood and Company, Baltimore, 1937.

The author takes up again the subject of avoidance of infection, Chapter XXI, and reiterates and expands the details. Under anesthesia he says, "the most striking development in recent years, however, is the increasing favor with which spinal anesthesia is viewed." It is evident that Dr. Kerr also regards this method with favor. Chloroform is evidently the anesthetic of choice for house practice in the British Isles. Ten pages are devoted to amnesia and analgesia in labor. The subjects of version, forceps, mechanical enlargement of the pelvis, and cesarean section are comprehensively discussed, especially, in regard to the low segment operation with which the author's name is so intimately connected. Modifications, complications, and accessory operations in connection with cesarean section are described. There is ample description of the operative aspects of the various types of puerperal hemorrhages and the use of the blood transfusions is emphasized repeatedly in this connection. Separate sections are devoted to the traumatic conditions associated with operative delivery and obstetric shock, as well as to the injuries sustained by the child. Kerr, whose interest in maternal morbidity and mortality has led to a separate publication on that subject, quotes frequently on the statistical aspects of the morbidity and mortality attending the operative handling of abnormal labors.

This edition of Kerr's *Operative Obstetrics* is outstanding as a work of practical utility and as a reference book. It merits the highest praise.

—*Philip F. Williams.*

Brindeau and Lantuéjoul offer in *La Présentation Du Siège. La Version*[3] an extended dissertation on the operative methods of delivery in a breech presentation, and also consider the technic of version. The book is divided in two parts, 75 pages of text, and 92 full page illustrations by Lemeunier.

The attitude of the authors toward this condition when discovered in pregnancy is one of laissez-faire. The authors feel that external version is difficult to accomplish in a primipara, and unnecessary in a multipara. The normal mechanism of breech is clearly described; the authors regard the breech as having three distinct phases, the pelvis, the shoulders, and the after-coming head, all of which should be considered in relation to the inlet, cavity, and outlet. Following very definite and conservative indications for interference, the generalities and the details of the technic of extraction are given. The method of Mauriceau is preferred to forceps in the usual run of cases. The difficulties encountered in extraction as well as the complications are well covered. Cesarean section in breech presentation is regarded as preferable to a difficult vaginal delivery, and may be indicated even after a trial labor. The relation of breech delivery to placenta previa is discussed. The authors conclude that a breech baby stands asphyxia better than traumatism, and that most complications are produced by the attendant.

The subject of version takes up both external and internal methods, and combined. Prophylactic version, "Méthode préconisée par les Americains," is rejected. The treatment of the subject is thorough and clear; particular stress is laid on the contraindications, dangers, and possible complications.

The ninety-two page illustrations by Lemeunier are beautifully executed. Many have from one to four insets showing details of a particular step in the operative procedure. Seemingly every possible complication and the appropriate maneuver are portrayed. The same may be said of the illustrations depicting version. There are included a number of roentgenographs or photographs of fetal injuries which may be sustained in the operations discussed.

This book with its complete discussion and superb illustrations is warmly commended.

—*Philip F. Williams.*

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[3]**La Présentation Du Siège. La Version.** Par A. Brindeau, Professeur de Clinique Obstétricale et Gynécologique et P. Lantuéjoul, Accoucheur des Hôpitaux, Faculté de Médecine de Paris. Avec illustrations, Pl.XCII. Vigot Frères, éditeurs, Paris, 1937.

Vignes has withdrawn for separate publication his article on the physiology of *Gestation*[4] which appeared in the second edition of the textbook on physiology edited by Roger and Binet. In this section he has developed the material under three rubrics: the physiology of the embryo and fetus, physiology of the placenta and membranes, and the modifications and alterations of function experienced by the pregnant organism. With graphs, charts, and tables he illustrates the growth and development of the child, and its constituents of a mineral nature. He remarks particularly on the inconstancy of the accepted signs of fetal maturity. In discussing immunizing substances, he feels that the complement content of the fetal blood is nil or very little, and that what immunity the newborn child has is a passive one. He feels that it is possible for an antigen to traverse the placenta. He regards the blood of the newborn as not being separable into groups. There is an excellent discussion of the interrelationship of the fetal pancreas and maternal blood sugar, especially if diabetes exists in the woman.

The physiology of the placenta in the light of recent researches is fairly discussed, and the author develops at length the newer physiology of pregnancy in regard to the glands of internal secretion, as well as giving very complete dissertations on the physiology of the other systems.

—Philip F. Williams.

This book, *Maladies des Femmes Enceintes, Affections des Muqueuses Génitales,*[5] forms the fourth of a series of monographs on the complications of pregnancy.

In this volume Vignes discusses at length the diseases of the cervix, vagina, and vulva. The various infections, infestations and newgrowths of these three areas are described and discussed, not alone from the standpoint of pathology and therapeutics, but upon their relation to the physiology and pathology of pregnancy.

The subject of trichomonas infestation occupies eight pages of text, which offers an idea of the comprehensive manner in which the various topics are discussed. This is an excellent reference book, with a very large bibliographic reference index.

—Philip F. Williams.

In this *Maladies des Femmes Enceintes, Affections de la Peau,*[6] the third in a series of monographs discussing the systemic complications of pregnancy, Vignes particularizes on the lesions of the skin. The text shows that a wide review of the literature has been made and the subject matter covers the entire field of cutaneous medicine. This book forms an excellent reference volume.

—Philip F. Williams.

Vignes[7] offers a well-arranged bibliography of his surprisingly numerous contributions to all branches of obstetrics, gynecology, and other subjects. There are more than 700 titles in which are included numerous books. Both clinical and laboratory investigations have been performed by this very fecund author whose style is most readable, whose search of the literature is minute and whose breadth of knowledge is amazing.

—R. T. Frank.

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[4]**La Gestation.** Par H. Vignes. 211 pages. Masson et Cie, Paris, 1936.

[5]**Maladies des Femmes Enceintes, IV, Affections des Muqueuses Génitales.** Par Henri Vignes, Professeur agrégé à la Faculté de Médecine. Accoucheur des Hôpitaux de Paris, Masson et Cie, Paris, 1937.

[6]**Maladies des Femmes Enceintes, Affections de la Peau.** Par Henri Vignes, Professeur agrégé à la Faculté de Médecine, Accoucheur des Hôpitaux de Paris, Masson et Cie, Paris, 1937.

[7]**Exposé des Titres et des Travaux Scientifiques.** By Dr. H. Vignes. 197 pages. Masson et Cie, Paris, 1937.

Included in *Leçons du Jeudi Soir a la Clinique Tarnier*[8] are fourteen essays bearing on gynecology and obstetrics, which may be regarded as reflecting present-day French teaching and practice. Brindeau contributes a lengthy article on a genetic topic, "Congenital Hypognathism"; Ecalle has a meritorious contribution on the nonfebrile complications of the puerperium. Brouha discusses cancer of the cervix complicating pregnancy; he has observed three instances of this association recently. Among the remaining essays one must mention Gilbert's excellent discussion of roentgen therapy in myoma and Lantuéjoul's contribution on breech presentations in primiparas.

This year's papers compare most favorably with previous collections and sustain the high esteem in which the Clinic Tarnier is held in the obstetric world.

—*Philip F. Williams.*

Dr. Vaughan's interest in the sacrifice of life coincident with childbirth has caused her to make a wide study of the causes of difficulty in parturition. She has published the results of her inquiries in this book entitled, *Safe Childbirth: The Three Essentials; Round Brim, Flexible Joints, Natural Posture,*[9] and concludes, as the title indicates, that these three essentials make for the safety of the mother and child. She discusses the problem of difficult childbirth particularly from the standpoint of mortality. Later in this part of the book she narrates the manner of care in delivery among the Andaman tribes, the various castes of Hindus and the countries of Europe.

She considers the cause of difficult childbirth to lie primarily in the unyielding pelvis, and states that the shape of the brim determines the capacity of the pelvis, and that a larger fetal head can be born through the pelvis with a circular brim than through any other shape of inlet of the same boundary measurements. She regards the pelvis with the circular brim as the only normal pelvis in women of all races. The most frequent alteration of the round pelvis she feels is the oval brim, and the etiology of this deviation is ascribed to bone disease, improper posture and absence of sunshine. It is asserted that a rough estimate of the pelvic shape and capacity can be predicated by the woman's shape and position of her teeth and jaws. The author discusses, and illustrates by roentgenographs, the influence of posture on the pelvic joints and pelvic measurements.

To obtain the normal pelvis as described by Dr. Vaughan it is necessary to begin with intrauterine life, and after birth to follow the child through infancy and adolescence constantly overseeing the diet and posture.

Finally, when parturition ensues in a woman so cared for, she should be allowed to adopt the squatting position and other postures commonly used among primitives. The author narrates experiences with a group of women who practiced exercises during the pregnancy to enlarge the pelvic joints, and in labor used the postures suggested.

In concluding this review, a sentence from the foreword, written by Dr. Howard A. Kelly, may be quoted, "Whether all the doctor's conclusions are at once accepted or not, it is of vital importance that they be most carefully considered and duly weighed."

—*Philip F. Williams.*

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[8]**Leçons du Jeudi Soir a la Clinique Tarnier.** Avec 70 figures. Vigot Frères, éditeurs, Paris, 1937.

[9]**Safe Childbirth.** The Three Essentials. By Kathleen Olga Vaughan, formerly Medical Officer, Egyptian Quarantine, etc. With foreword by Howard A. Kelly. Illustrated, 154 pages. William Wood and Company, Baltimore, 1937.

The late George Davis Bivin, who was particularly interested in the prophylaxis of psychoneurosis and psychoses in children, had in the course of his researches become interested in the subject of *Pseudocyesis,*[10] and had collected a great amount of material on this subject previous to his death. This material has been edited by his associate, Miss Klinger. The early conception of this condition held by Bivin is that it should be looked upon as a conversion hysteria, a functional disturbance. Later, he formulated the hypothesis that pseudopregnancy, a normal state in the menstrual cycle, becomes pseudocyesis, an abnormal state, because the hormones which regulate this phenomenon are thrown out of balance by physical or emotional changes, or a combination of these two factors. Since he drew no conclusions regarding his theories, this material has not been incorporated in this work.

Miss Klinger presents an analysis of the cases studied, which represent an enormous collection of references to this condition. The literature was reviewed as far back as 1721 at which time an article by Mauriceau appeared. Every symptom in each case, which the reporting physician had specifically mentioned, is tabulated. In the chapter on symptomatology the occurrence and disturbance of these symptoms is discussed. In the order of relative frequency, with which the various organs or physical conditions were mentioned, it is noted that the menstrual changes had a relative frequency of 100, abdominal changes of 99, breast changes 93, fetal signs 79, uterine contractions 50. The comments of the reporters of these various cases on diagnosis form the text of the succeeding chapter. Miss Klinger gives an interesting historic résumé of the etiologic theories beginning with the observation of Hippocrates, continuing with those of Mauriceau, Parvin, Mitchell, and Liepmann, the latter developed a threefold cause which he based in part on Pavlov's experiments. Further, she discusses the reason for certain specific symptoms as interpreted from the reported cases. Among the therapeutic measures employed there are included twelve instances where curettage was used and ten instances where surgery of the pelvic organs was performed. In a number of cases treatment was accomplished by insertion of a catheter in the bladder.

Miss Klinger concludes that pseudocyesis is a psychoneurotic condition probably best classified as an hysteria, for which the most successful treatment is destroying the patient's conviction of her pregnancy. The bibliography of case reports takes up fifteen pages.

—*Philip F. Williams.*

In a preceding publication Nevinny had advanced valid proof that such mechanical factors as venous stasis definitely play a rôle in the actual causation of certain types of cerebral birth injuries. Such stasis as a rule is due to a state of intrauterine asphyxia. In this study entitled *Medicamentous Relief of Intrauterine Asphyxia*[11] Nevinny presents conclusions based on experimental investigations and clinical observations. Inhalation anesthesia can relieve fetal asphyxia caused by exaggerated uterine activity, ether in this respect offering certain advantages over chloroform. However, in a larger number of instances fetal heart action more effectively is improved by drugs directly influencing circulation, especially by Cardiazol. This drug also seems to prevent uterine overactivity. It proves useful in strengthening fetal cardiac action preceding operations, thus reducing the harmful effect if operative intervention on the child is required.

—*Hugo Ehrenfest.*

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[10]**Pseudocyesis.** By George Davis Bivin, Ph.D. and M. Pauline Klinger, M.A. The Principia Press, Inc. Bloomington, Indiana, 1937.

[11]**Medikamentoese Bekaempfung der Intrauterinen Asphyxie.** Von Dr. med. habil. H. Nevinny, Universitaets-Frauenklinik, Koenigsberg. Pr. Mit 48 Textabbildungen, 104 Seiten. Ferdinand Enke, Stuttgart, 1937.

This delightfully fascinating story of childbirth, *Into This Universe*,[12] has evidently been prepared for laymen but all physicians will find Dr. Guttmacher's story of intriguing interest and well worth reading.

The imaginative recital of Ambroise Paré and his version on Marguerite de Puis in the sixteenth century, is an epic. It signalizes the beautiful manner with which Dr. Guttmacher has traveled through the obstetric folk-lore of the ages, with wide ranges in the literature of both lay and medical sources of different epochs and countries, to illustrate the history of childbirth. And so through the problems of the diagnosis of pregnancy, the physician's observations and the modern laboratory tests, we find a continuing recital of the development of modern science. In the section on pregnancy, the lay person will find not only an explosion of the theory of maternal impressions, but a safe and sane exposition of the principles of present-day prenatal care.

The story of labor, written in a fully explanatory manner, should in no sense alarm any woman who might read the chapters, but should convey to her a complete yet reassuring explanation of what actually happens when a baby is born, even to the discussion of the obstetric operations. In a like manner the subject of the puerperium and the newborn child is discussed. In marked contrast to the not infrequent diatribes on maternal mortality in lay journals is the exceedingly sane, although frank, discussion of morbidity and mortality in the chapter entitled "Safer Childbirth."

We may all hope with Dr. Guttmacher that, with study and progress, the many problems of obstetrics may soon be solved. The documentation of the book is thorough, and the list of contributions and books in the bibliography should be of interest to all who wish to read further in this story of childbirth.

—*Philip F. Williams.*

In this historical chronicle, *Childbirth: Yesterday and Today*,[13] Dr. Rongy describes the attitude of various peoples and ages toward maternity. This fascinating story is presented in simple language and should be of interest as much to physicians as to the public, for whom it seems to have been intended.

Primitive practices and customs among the Orientals and later the Greek and Roman peoples evidence how long this natural function has been shrouded in mystery and ignorance. Rongy describes the early awakening of scientific medicine in the fifteenth and sixteenth centuries and explains how these advances were soon reflected in obstetrics. There is an interesting account of the early operative developments in obstetrics, including the story of the Chamberlen family and their forceps.

He passes on to the work of Holmes and Semmelweis, Gordon and White, and stresses the point that puerperal sepsis is still the great cause of death in the parturient. The development, place in society, and present status of the midwife forms an interesting chapter. Rongy points to the gradual elimination of this factor in obstetric work. In discussing child care and the methods used among many people he shows the gradual influence of the development of scientific medicine. He brings in chapters on the mystery of birth, and the place of the father as regards delivery among different peoples. He relates that birth control was the practice among both the ancient Hebrews and Greeks and comments on the continuance of this practice in our modern times. He feels that, ultimately, contraceptive birth control will be legally sanctioned. Finally, he discusses the modern practice of obstetrics with its overspecialization, and, as far as the United States is concerned, the factors bearing on the high maternal mortality rate.

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[12]**Into This Universe.** The Story of Human Birth. By Alan Frank Guttmacher, Associate in Obstetrics, Johns Hopkins University, Illustrated, 366 pages. The Viking Press, New York, 1937.

[13]**Childbirth: Yesterday and Today.** By A. J. Rongy, M.D., Attending Obstetrician and Gynecologist, Lebanon Hospital, etc. With 20 illustrations, 192 pages. Emerson Books, Inc., New York, 1937.

As stated above, this delightfully written historical account of obstetrics should be of value not only to the lay person but to the physician as well.

—*Philip F. Williams.*

In this small volume, *Safely Through Childbirth*,[14] Dr. Rongy describes the story of pregnancy and childbirth for the lay audience in the hope that it will contribute to a greater understanding of this fundamental aspect of science.

Simply, but clearly, he discusses anatomy, conception, and the physiology of pregnancy. There is a very sane discussion, useful for doctors as well as the laity, of relief of pain in labor. The section on prenatal care, although short, is quite thorough. The various types of operative deliveries are briefly touched upon. Dr. Rongy missed an excellent opportunity to do a little missionary work when he failed to discuss criminal abortion, and its often tragic consequences. A philosophic description of the menopause completes the work. This book is well suited for lay education in obstetrics.

—*Philip F. Williams.*

The widespread campaign for the improvement of *Maternal Care*[15] showed a need for the concise statement of the principles of antepartum, intrapartum, and postpartum care. It is felt that this handbook prepared by a group of members of the American Committee on Maternal Welfare will amply supply the needs of the average practitioner of obstetrics. The material is simply and directly presented with emphasis on the cardinal principles and insistence on the nearest approach to asepsis which is possible, and a short and direct discussion of obstetric operations and complications.

It is hoped that this handbook will have a wide distribution among general practitioners, hospital internes, and public health nurses.

—*Philip F. Williams.*

The 1936 report of the *Obstetric Clinic of the Hospital of San Juan de Dios*[16] of which the chief is Professor Del C. Acosta, is submitted. This covers a report of 1,846 patients. In addition to the statistics, it contains a number of papers on various subjects, mainly clinical, such as tumors in pregnancy, anesthesia, the treatment of septic abortion by means of sera, and a casuistic such as two cases of infected fibroids during the puerperium. Judging by this report, syphilis is very prevalent among pregnant women in Colombia.

—*R. T. Frank.*

For the first time, as far as we are aware, the subjects of *Obstetric and Gynecologic Nursing*[17] have been combined in one book. In recognition of the changing trends in nursing education the authors, Dr. Falls and Miss McLaughlin, have written this book to encompass the varying situations in which obstetric, as well as gynecologic, nursing finds a field.

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[14]**Safely Through Childbirth.** By A. J. Rongy, Attending Obstetrician and Gynecologist, Lebanon Hospital, etc. With 20 illustrations, 192 pages. Emerson Books, Inc., New York, 1937.

[15]**Maternal Care.** The Principles of Antepartum, Intrapartum, and Postpartum Care for the Practitioner of Obstetrics. Approved by the Committee on Maternal Welfare, Inc. By Dr. Fred L. Adair, Editor. The University of Chicago Press, Chicago, Ill.

[16]**Boletin Anual 1936. Clinica Obstetrica, Hospital de San Juan de Dios.** Bogota, Colombia.

[17]**Obstetric and Gynecologic Nursing.** By Frederick H. Falls, M.D., Professor of Obstetrics and Gynecology, University of Illinois, College of Medicine, etc. and Jane R. McLaughlin, Supervisor of the Department of Obstetrics and Gynecology, Research and Educational Hospital, etc. With 83 illustrations, 492 pages. The C. V. Mosby Company, St. Louis, 1937.

So in this book are assembled ample instruction on the theory and practice of both branches, as well as specialized information for the institutional nurse working under organized systems, the family nurse serving the general practitioner in home practice, as well as the needs of the public health nurse either on urban or rural assignments.

The material on obstetrics is presented in a simple, easily understandable manner, and with a logical sequence of subjects. It is very possible that there is a slight overbalance at times, as for instance, the space devoted to the mutilating operation on the fetus. Two sections are worthy of special notice, the chapter on the outpatient nursing services and that on the nurse in the home delivery. If in the latter situation a capable nurse is cooperating with the physician, it is a blessing and benefit. The section on gynecology and gynecologic nursing leaves little to be desired. The theory is short, concise, and medically authentic. The nursing procedures detailed and discussed are those of particular use in the surgery or treatment of pelvic lesions.

—Philip F. Williams.

In preparing the present eleventh edition of his *Obstetrics for Nurses*[18] DeLee has obtained collaboration of Mabel C. Carmon, R.N., and her name appears as co-author. This book has been so favorably received over a period of thirty-three years that an extended review seems unnecessary.

The chapter on hospital obstetrics has been rewritten by the co-author, to present a fuller consideration of institutional technic, while new material has been introduced in various other chapters. The chapter on hospital obstetrics is, in miniature, a very complete manual of the care of the parturient woman from her admission in labor until she is sent to her ward or private bed.

The duties of the personnel, the preparation of material used, the set up of instrument trays for normal and operative deliveries, and the administration of medicine are detailed. DeLee suggests the use of palm prints on dactyloscript as a more permanent means of identification of the newborn infant than sole prints.

There is every evidence that the present edition will maintain the long and well-deserved popularity of its predecessors.

—Philip F. Williams.

This little book is written by a man of experience in country practice from a town with a population of eleven thousand. This *Physicians' Guide Book for Mothers*[19] gives a simple and concise set of directions as to prenatal care and care after delivery. The third chapter discusses the final examination after delivery, which he might possibly term the follow-up examination. He adds some very pertinent observations of the necessity of the cooperation of the public with the physician in maternity work, and stresses the danger signals of complications which may arise in pregnancy or the puerperium.

On the title page are entries of the woman's name and address. The appendices include perforated pages for the physician to fill out and upon which he may note the prenatal and delivery record. An omission is that the pelvic measurements are not listed. Following the weight record of the mother are pages upon which special directions, notations for supplies and questions on the care of the mother and the baby may be entered.

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[18]**Obstetrics for Nurses.** By J. B. DeLee, A.M., M.D., Professor of Obstetrics and Gynecology, Emeritus, University of Chicago, Consultant in Obstetrics, Chicago Lying-In Hospital and Dispensary; Consultant in Obstetrics, Chicago Maternity Center, and Mabel C. Carmon, R. N., Chief Supervisor and Instructor in the Birth-rooms, Chicago Lying-In Hospital and Dispensary. Eleventh Edition with 291 illustrations, 659 pages. W. B. Saunders Company, Philadelphia and London, 1937.

[19]**Physicians' Guide Book for Mothers.** By G. G. Keener, M.D. Southern Publishers, Inc. Kingsport, Tenn., 1936.

It might be well that some of the Social Security funds devoted to maternal welfare be used in distributing samples of this book throughout the rural areas of the United States.

—*Philip F. Williams.*

This fine book, *Getting Ready to Be a Mother,*[20] by Miss van Blarcom has reached its third edition. In this edition new material on habit training and other topics has been added. The first half of the text is a well-considered presentation of prenatal care and of preparation for labor.

The second half is an excellent manual on baby care in all its multitudinous details. Several appendices describe the physiology of reproduction. The language used is clear and concise, the statements made are direct and medically correct. One feels that the average woman who is getting ready to become a mother will get much help from reading this book, and incidentally will be likely to cooperate more fully with her medical attendant.

—*Philip F. Williams.*

Newborn, Infants, and Children

Tow's *Diseases of the Newborn*[32] is designed mainly for the general practitioner but should be of interest to the pediatrician as well. It deals with the first month of life. There is much valuable data in the chapter on general considerations. The author advises intramuscular injection of camphor in oil to inhibit lactation in the mother. For pylorospasm, atropine, phenobarbital and calcium are indicated. Any newborn infant under 5 pounds in weight is considered premature. Treatment in this group has little effect on the number of deaths occurring within forty-eight hours postpartum.

In the chapter on birth injuries, it is stated that the majority of diplegias are due to the pathologic process of intrauterine origin. By no means will all obstetricians agree with this point of view. The disorders of the various systems are taken up in order, the skeletal, the genitourinary, the nervous system; then eye, ear and nose; and finally the septic and infectious diseases.

Of particular interest to the gynecologist are the cases and references under female genital tract. For example, a case of prolapse of the uterus at birth combined with other deformities; mixed tumors of the vagina and similar genital disturbances noted at birth.

Whether such a statement as "an equable state of mind on the part of the mother is the most important single factor in the production of good breast milk" can be accepted in view of our present endocrine knowledge is more than doubtful. The book is well written, and each chapter concludes with a good bibliography.

—*R. T. Frank.*

Birth Injuries of the Central Nervous System[33] are thoroughly discussed by H. Nevinny in this small monograph. After surveying the very extensive literature on the subject the author analyses in detail a comparatively large material consisting of 153 cases that have been autopsied. In general, his findings and con-

[20] **Getting Ready to Be a Mother.** By Carolyn Conant van Blarcom, R.N. Third edition, revised. With 97 illustrations, 305 pages. The Macmillan Company, New York, 1937.

[32] **Diseases of the Newborn.** By Abraham Tow, M.D., Adjunct Professor of Pediatrics, New York Polyclinic Hospital, etc. Illustrated, 477 pages. Oxford University Press, New York, 1937.

[33] **Die Geburtstraumatischen Schaedigungen Des Zentralnervensystems.** Von Dr. Med. H. Nevinny, Universitaets-Frauenklinik in Koenigsberg, Pr. Mit 8 Textabbildungen und 12 Tabellen. 87 Seiten. Ferdinand Enke, Stuttgart, 1936.

clusions in regard to causative factors harmonize well with those announced by other writers. Of special interest, however, is the emphasis he lays on the possible prevention of intrauterine asphyxiation by two means, readily available, namely, administration of the cardiac stimulant cardiazol, or slight inhalation anesthesia when uterine contractions are severe or follow each other too quickly. He feels certain that in this manner many infants can be protected against cerebral injuries. It seems superfluous to add that the diagnosis of injury to the central nervous system can be made or excluded only if the autopsy is extended to a study of the spinal cord throughout its entire length.

—Hugo Ehrenfest.

Torild Brander from Finland has written a monograph on the *Development of Intelligence in Premature Children.*[34] These children were investigated between the seventh and fifteenth year from both a physical as well as a neuropsychical point of view. Such a study will probably be feasible only in small countries where the population is sessile.

Where the birth weight was under 2,500 gm. the case was classified as premature. Previously investigators used various criteria. If the I.Q. is employed, more defectives are noted. His material was based on 18,000 births of which 12.8 per cent were premature, a total of 2310. Of these, 1240 died before the mother was discharged from the clinic, 1070 children being discharged. Of these, 240 died subsequently; 583 were found alive in the age period of seven to fifteen years.

The Binet-Simon-Terman tests were employed throughout; 376 cases could be examined. Of these, 86 were twins, 22.9 per cent. Of the twins (42 pairs), 11 twins showed weakmindedness, 22.6 per cent. Of 290 single births, 31 or 10.7 per cent showed weakmindedness. Of all the children examined, 46 per cent were found normal in intelligence, 56.7 per cent below standard, 1.4 above standard, and 11.2 per cent distinctly weakminded.

Birth weights between 1,000 and 1,500 did not show a single normal child. Complications during labor increased the percentage of mental defectives. Children from low social groups showed a depressed I.Q. In the general population 12.5 to 25 per cent of all mental deficiencies are ascribed to premature birth. An interesting casuistic section and a number of illustrations add further value to this important contribution.

—R. T. Frank.

In this little monograph, *Unreife und Lebensschwaeche,*[35] Peiper presents the story of the premature and immature baby. He notes that from 5 to 10 per cent of births fall in this class, of whom less than half reached the end of the first year of life. Regarding cause of such births it is noted, that in three very large series, the cause was undetermined in an average of 48 per cent, while syphilis, the next largest cause after multiple pregnancy, averaged 7.5 per cent. Various sections discuss weight, chemical values, hormone production and ferment content, physiologic manifestations, and cerebral deviations. External influences in development as nursing, infection, nutrition, are considered. Peiper regards a birth weight of 2,000 gm. as the basic limit for organic dysfunction. This monograph should be of interest to those concerned with the scientific aspects of the problem of immaturity.

—Philip F. Williams.

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[34] **Studien Ueber Die Entwicklung Der Intelligenz Bei Fruehge borenen Kindern.** Von Torild Brander. Mit 58 Abbildungen und 67 Tabellen nebst tabellarischen Beilagen. Helsingfors, 1936.

[35] **Unreife und Lebensschwaeche.** Von Professor Dr. Albrecht Peiper, Wuppertal. Mit 10 Abbildungen, 103 Seiten. Verlag von Georg Thieme, Leipzig, 1937.

The necessity for another edition of *Diseases of Infants and Children*[36] gave Griffith and Mitchell an opportunity to make many important changes in this volume, which had met with universal and prompt approval at the time of its appearance. Much new material has been added in the chapters dealing with anatomy, physiology, and growth of the newborn and young infant, artificial feeding, disturbances of acid-base balance, dehydration, and many other conditions. We mention the foregoing topics in particular because we feel that every physician doing obstetric work of necessity must be informed on these aspects of pediatrics and because we know of no other textbook which deals with the entire subject better than this volume.

—*Hugo Ehrenfest.*

Society Transactions

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF MAY 6, 1937

The following papers were presented:

The Management of Pregnancy and Labor Complicated by Triplets. Dr. John C. Hirst. (This article will appear in a later issue.)

Myxedema With Menorrhagia and Tetany as Complications Following a Partial Thyroidectomy. Dr. Charles W. Dunn, and Dr. William R. Nicholson. (For original article, see page 164.)

The Basal Metabolic Rate in Normal Pregnancy. Dr. George C. Hanna, Jr. (For original article, see page 155.)

Items

American Board of Obstetrics and Gynecology

The next examination (written and review of case histories) for Group B candidates who have filed applications will be held in various cities of the United States and Canada, on Saturday, February 5, 1938.

The general oral, clinical and pathological examinations for all candidates (Groups A and B) will be conducted by the entire Board, meeting in San Francisco, California, on June 13 and 14, 1938, immediately prior to the meeting of the American Medical Association.

Applications for admission to the June, 1938, Group A examinations must be on an official application form and filed in the Secretary's Office before April 1, 1938.

For further information and application blanks address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pa.

[36] **The Diseases of Infants and Children.** By J. P. Crozer Griffith, Emerit. Professor of Pediatrics, University of Pennsylvania, etc. and A. Graeme Mitchell, Professor of Pediatrics, College of Medicine, University of Cincinnati, etc. Second edition, revised and reset. 1154 pages. W. B. Saunders Co., Philadelphia, 1937.

American Association of Obstetricians, Gynecologists, and Abdominal Surgeons Annual Prize

The American Association of Obstetricians, Gynecologists, and Abdominal Surgeons has recently announced a new annual prize of $500.00. Those eligible include only (1) internes, residents, or graduate students in obstetrics, gynecology, and abdominal surgery, and (2) physicians (M.D. degree) who are actually practicing or teaching obstetrics, gynecology, or abdominal surgery.

Competing manuscripts must (1) be presented in triplicate under a *nom-de-plume* to the Secretary of the Association before June 1, (2) be limited to 5,000 words and such illustrations as are necessary for a clear exposition of the thesis, and (3) be typewritten (double-spaced) on one side of the sheets, with ample margins.

The successful thesis must be presented at the next annual (September) meeting of the Association, without expense to the Association and in conformity with its regulations.

For further details, address Dr. James R. Bloss, Secretary, 418 11th Street, Huntington, West Virginia.

Officers of American Association of Obstetricians, Gynecologists and Abdominal Surgeons

The following Officers were elected at the annual meeting held in September, 1937:

President—Dr. Paul Titus, Pittsburgh, Pa.
President-Elect—Dr. James E. King, Buffalo, N. Y.
Vice President—Dr. Albert Mathieu, Portland, Ore.
Secretary—Dr. James R. Bloss, Huntington, W. Va.
Assistant Secretary—Dr. LeRoy A. Calkins, Kansas City, Mo.
Treasurer—Dr. Lewis F. Smead, Toledo, Ohio.
Members of the Council for three years:
Drs. James W. Kennedy, Philadelphia, Pa., and W. Wayne Babcock, Philadelphia, Pa.

International Congress of Obstetrics and Gynecology
Amsterdam, May 4 to 8, 1938

Under the Patronage of H. M. the Queen of the Netherlands

Honorary Chairmen

Dr. H. Colijn, Prime Minister and Minister of Foreign Affairs.
Prof. Dr. J. S. Slotemaker de Bruïne, Minister of Public Institution.
Mr. Dr. A. Baron Röell, Governor of the Province of Noord-Holland.
Dr. W. de Vlugt, Burgomaster of Amsterdam.

President

Prof. Dr. A. H. M. J. van Rooy, Director of the University Clinic of Obstetrics and Gynecology.

Secretary

Dr. F. C. van Tongeren, Deputy Director of the University Clinic of Obstetrics and Gynecology.

PRELIMINARY PROGRAM

TOPICS FOR DISCUSSION

I. Eclampsia. II. Thrombosis and Embolism. III. Hormones.

Reporters:

I. Pathogenesis, Treatment, Dr. E. Klaften, Vienna, Dr. H. Vignes, Paris, and Prof. B. Stroganoff, Leningrad
Eclampsia, from a geographical point of view, Prof. K. de Snoo, Utrecht, and Prof. R. Remmelts, Batavia

II. Diagnosis and Symptomatology, Etiology, Prevention and Treatment, Prof. E. Cova, Torino, Prof. D. Dougal, Manchester, Prof. S. E. Wichmann, Helsinki

III. Historical review, Prof. G. Wagner, Berlin, and Prof. C. Kaufmann, Berlin
Lecture on latest research, Dr. C. Hartman, Baltimore, and Prof. L. Brouha, Liège

Discussors: Dr. M. Cheval, Brussels. Prof. C. Cotte, Lyon. Prof. F. Daels, Gent. Prof. J. Engelhard, Groningen. Prof. L. Fraenkel, Sao Paulo. Prof. J. Frigyesi, Budapest. Prof. P. Gaifami, Roma. Prof. G. Gheorghiu, Bucaresti. Dr. J. Greenhill, Chicago. Prof. H. Guggisberg, Bern. Prof. E. Hauch, Copenhague. Prof. P. van der Hoeven, Leiden. Prof. Dame A. L. McIlroy, London. Prof. M. Jayle, Paris. Dr. J. Jensen, St. Louis. Prof. H. Kahr, Vienna. Dr. A. Laffont, Alger. Prof. E. Laqueur, Amsterdam. Dr. J. DeLee, Chicago. Prof. W. Liepmann, Istanbul. Prof. N. Louros, Athen. Dr. A. Manevitch, Moscou. Prof. H. Martius, Göttingen. Prof. A. Mayer, Tübingen. Prof. M. Phillips, Sheffield. Prof. R. Schröder, Leipzig. Prof. B. Solomons, Dublin. Dr. F. Taussig, St. Louis. Prof. A. Westman, Lund. Prof. B. Zondek, Jerusalem.

Visitors are advised to apply to the Travel agencies Wagons-Lits/Cook, for reduced fares and for reserving hotel accommodation. Rooms (breakfast, tips and taxes included) can be obtained at prices ranging from D.Fl.3.50 to D.Fl.6.25.

Meetings Will Be Held at the Koloniaal Instituut

Evenings are fixed for receptions, a visit to the Castle "Nijenrode" and Closing Banquet.

On May 8 and 9 there are various trips on the program, including the Reclaiming Works of the "Zuiderzee." A concert, at the "Concertgebouw," by the famous conductor Willem Mengelberg (eighth Symphony of Mahler) has also been arranged. There is also a special program for ladies.

Prospective visitors may become members of the Congress by subscription at the following rates: full members, 15 Dutch florins, associate members (including family), per person, 5 florins. Address the Treasurer, Dr. I. J. Wijsenbeek, "Postgiro rekening, 294741, Amsterdam, Holland.

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Little Rock

Hinkle, S. B.

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Vollmer, A. M.

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GILLIS, R. A. D.
GOLDSTEIN, SAMUEL
HEPP, J. A.
KATZ, DAVID
NUCCI, ROSARIO C.
REEVES, T. K.
STEVENSON, J. W.
TITUS, PAUL

Punxsutawney

BENSON, JOSEPH P.

Washington

RUBEN, SAMUEL A.

Wilkes-Barre

KOCYAN, J. J.

Rhode Island

Providence

APPLETON, PAUL
BUXTON, BERTRAM H.
HALE, F. S.
MATTEO, F. I.
POTTER, ALFRED L.
WALSH, JOHN G.
WATERMAN, GEORGE W.

South Carolina

Charleston

MCCRADY, R. L.
WILSON, L. A.

Tennessee

Cookeville

RING, H. H.

Memphis

BLACK, W. T.
PRIDE, W. T.
REINBERGER, J. R.
RUCH, W. A.
SCHREIER, P. C.
*TOOMBS, P. W.

Nashville

BURCH, L. E.
LEWIS, M. S.

Texas

Dallas

BOURLAND, J. W.
HANNAH, C. R.
SACHER, C. B.

Fort Worth

GROGAN, R. L.

Galveston

COOKE, W. R.
ROBINSON, H. R.

San Antonio

MAXWELL, W. W.
PASSMORE, B. H.

Vermont

Burlington

DURFEE, HERBERT A.
EASTMAN, O. N.

Virginia

Newport News

PAYNE, WAVERLY R.

Norfolk

ANDREWS, C. J.
THORNHILL, P. E.

Portsmouth

WALKER, ALBERT T.

Richmond

BAUGHMAN, GREER
GRAY, B. H.
RUCKER, M. P.
WHITFIELD, JAMES M., JR.

University

WILLIAMS, T. J.

Washington

Seattle

BELL, W. W.
THOMPSON, G. G.

West Virginia

Huntington

BLOSS, J. R.

Wisconsin

Madison

CAMPBELL, R. E.
HARRIS, J. W.
THORNTON, MADELINE J.

Milwaukee

DARLING, F. E., JR.
HORWITZ, J. J.
MCDONALD, ROBERT E.
SURE, JULIUS H.
URDAN, BENJAMIN E.

Canada

London

SHUTE, E. V.

Montreal

*LITTLE, H. M.

Toronto

CANNELL, D. E.
*CLELAND, F. A.
GOLDSTEIN, JACOB
HARRIS, L. J.
HENDRY, W. B.
SCOTT, W. A.
VAN WYCK, H. B.

Syria

Bierut

DORMAN, H. G.

Total 737

*Deceased.